1/7/98

MEMORANDUM

DATE: 1/7/98

SUBJECT: PP#7F04832. Fipronil in/on Rice. **HED Risk Assessment.** Chemical 129121. Barcodes D239007. Case 061662.

FROM: George F. Kramer, Ph.D.
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TO: Susan Lewis, Manager, PM Team 03
Ann Sibold, Reviewer, PM Team 03
Registration Division (7505C)

Rhône-Poulenc AG Company has submitted a petition for the establishment of permanent tolerances for residues of the insecticide fipronil in/on rice commodities. The proposed tolerances, expressed as fipronil [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile] and its metabolites MB 45950 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile]; MB 46136 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile]; and MB 46513 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile] are:

Rice, grain	0.02 ppm
Rice, straw	0.10 ppm

The present petition proposes to use an 80% water-dispersible granular (WDG) formulation (Product name = ICON™ 80 WG Insecticide), a 56% flowable solid (FS) formulation (Product name = ICON™ 6.2 FS Insecticide), and a 56% soluble concentrate (SC) formulation (Product name = ICON™ 6.2 SC Insecticide). Tolerances for residues of fipronil in/on and animal commodities have recently been established corn (40 CFR § 180.517(a)). The following are the tolerances for animal RACs (expressed as parent and metabolites MB 45950 and MB 46136):

Liver* ..... 0.10 ppm	Milk, fat ..... 1.50 ppm (reflecting 0.05 ppm in whole milk)
Fat* ..... 0.40 ppm	Eggs ..... 0.03 ppm
Meat* ..... 0.04 ppm	Poultry Fat ..... 0.05 ppm
Meat Byproducts ..... 0.04 ppm (except liver)*	Poultry Meat ..... 0.02 ppm
Hog Fat ..... 0.04 ppm	Poultry Meat Byproducts .. 0.02 ppm
Hog Meat Byproducts .... 0.01 ppm (except liver)*	Hog Liver ..... 0.02 ppm
	Hog Meat ..... 0.01 ppm

*of cattle, goat, horse and sheep

Fipronil is also currently registered for use on commercial turf and pets in the U.S. In addition, a petition for establishment of temporary tolerances in/on cottonseed and cottonseed processing fractions (PP#5G04583) is currently in reject status pending receipt of revised Sections B and F and proposed tolerances for milk and eggs (CBTS No. 16288, DP Barcode D219819, G. Kramer, 11/12/96).

A summary of the findings and an assessment of human risk resulting from the proposed use of fipronil are provided in this document. The hazard assessment was provided by Marion Copley, D.V.M. of RAB1; the product and residue chemistry data review by George Kramer, Ph.D. and Susie Chun of RAB1; the dietary risk assessment by Andrew Rathman of RAB1; the drinking water exposure assessment by Gail Maske of EFED; the occupational exposure assessment by Jeffrey Evans of RAB1.

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I. EXECUTIVE SUMMARY

HED has reviewed toxicology and residue data submitted by Rhône-Poulenc AG Company in accordance with the Federal, Fungicide, and Rodenticide Act (FIFRA) and 40 CFR §158, to support pending registration containing the active ingredient (ai) fipronil for use as an insecticide in/on rice.

The existing toxicity database supports the registration for fipronil technical and its photodegradate for use on rice with the exception of an acute inhalation study with the ICON™6.2FC formulation. This study will be considered a **TOXICITY CATEGORY I** until the new study is received and reviewed.

HED was requested to review several new studies on the parent **MB46030 (fipronil)**, metabolite **MB45897,** and **photodegradate MB46513**. The toxicity DERs will be submitted to RD with D237893. All studies were acceptable except as follows. The acute neurotoxicity study (81-8, MRID 44262808) is classified as unacceptable due the lack of positive control data. This study may be upgraded to acceptable upon the receipt and evaluation of adequate positive control data from the testing facility.

The Margin of Exposure (MOE) is a measure of how closely the anticipated exposure comes to the No Effect Level (NOEL). The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. HED's level of concern is for MOEs below 100 for fipronil.

Aggregate acute risk estimates do not exceed HED's level of concern. Using conservative exposure assumptions (TMRC), for the population subgroup of children (1-6 years old) the calculated Margin of Exposure (MOE) value for dietary (food only) exposure is 167. Potential residues in drinking water are not greater than HED's level of concern. The acute drinking water level of concern (DWLOC) for fipronil (+ metabolites including MB 46513) in children (1-6 years old) is 20 ppb. The peak (day-0) Tier I (GENEEC) estimated environmental concentrations for fipronil (+ MB 46136, MB 45950, and MB 46513) in drinking water was 2.271 ppb. HED concludes that there is a reasonable certainty that no harm will result from acute aggregate exposure to fipronil (+ MB 46136 and MB 45950) and MB 46513 residues for children.

Short-term aggregate margins of exposure (MOEs) do not exceed HED's level of concern. Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water (considered to be a background exposure level) plus indoor and outdoor residential uses. For the short- and intermediate-term aggregate risk of the most highly exposed subgroup (children 1-6 years), the calculated MOE is 270. There is a potential for short- and intermediate-term exposure from drinking water. However, as estimated average concentrations of fipronil in surface and ground water are less than OPP's levels of concern for drinking water as a contribution to chronic aggregate and chronic exposures, contribution to short- and intermediate- term exposure should not exceed OPP's levels of concern either.

Chronic aggregate risk estimates do not exceed HED's level of concern. Based on the available data and assumptions used for dietary/water/residential exposure and risk estimates, the population group estimated to be the most highly exposed to fipronil is non-nursing infants (< 1 year old) with a risk estimate from combined sources equaling 16.7% of the RfD. Chronic dietary exposure estimates for fipronil and MB 46513 utilized **anticipated residues**. For chronic exposure to fipronil (+ MB 46136 and MB 45950), the adult DWLOC is 6.67 ppb and for children (1-6 years old), the DWLOC is 1.77 ppb. Tier I (GENEEC) chronic EECs (56-day value) for fipronil (+ MB 46136 and MB 45950) were less than 0.9 ppb. For chronic exposure to MB 46513, the adult DWLOC is 0.69 ppb and for children (< 1 year old), the DWLOC is 0.19 ppb. Tier I (GENEEC) chronic EECs (56-day value) for MB 46513 were less than 0.01 ppb. HED thus concludes that there is a reasonable certainty that no harm will result from chronic aggregate exposure to fipronil (+ MB 46136 and MB 45950) and MB 46513 residues.

This chemical has been classified by the HED Cancer Peer Review Committee (document dated July 18, 1997) as a Group C - Possible Human Carcinogen, based on increases in thyroid follicular cell tumors in both sexes of the rat, which were statistically significant by both pair-wise and trend analyses. The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status. There was no apparent concern for mutagenicity (no mutagenic activity). Dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DRES chronic exposure analysis using the RfD.

Occupational exposure risk estimates do not exceed HED's level of concern. The MOE for mixer/loaders of the 80% WG formulation is > 1000; for mixer/loaders of the 1.5 G formulation, > 6000. There are no available data to assess the application of these products as soil incorporated insecticides. However, exposure during application is expected to be an order of magnitude lower than that of the mixer/loader. Therefore, the exposure while applying fipronil will not significantly impact the MOE.

The residue chemistry and toxicological data bases are adequate to support time-limited tolerances and a conditional registration for the use of fipronil on rice in terms of human health risk. HED recommends that the petitioner be required to submit: 1) the results of one additional rice field trial; 2) a revised section B; 3) a revised Section F amending the proposed tolerance for rice grain to 0.04 ppm; 4) a storage stability study for MB 46513; 5) an acute inhalation study with the ICON™6.2FC formulation; 6) the positive control data for the acute rat neurotoxicity study with the **photodegradate**; and; 7) a chronic study on the **photodegradate (MB 46513)**. To provide for the periodic evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) residue data be submitted every five years as long as the proposed tolerances remain in force. The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether fipronil share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for fipronil need to be modified or revoked.

II. BACKGROUND

Fipronil is a broad-spectrum insecticide belonging to the phenylpyrazole class of insecticides. Phenylpyrazoles affect the central nervous system of insects, apparently by blocking the γ-aminobutyric- (GABA-) regulated chloride channel. The proposed use on rice is intended to control the rice water weevil, an insect which feeds on the roots of rice plants in the larval stage and on the upper leaf surfaces in the adult stage. Larval damage in heavily infested fields results in reduced yields. Fipronil is currently used on rice in other countries (Thailand, China, and the Philippines).

Technical fipronil is to be formulated into a water-dispersible granular (WDG), a flowable solid (FS), and a soluble concentrate (SC) formulation.

Fipronil, also called MB 46030, is an insecticide. The toxicology data base for fipronil has previously been evaluated and was considered adequate to support registration for use on corn.

A **photodegradate, MB 46513,** has been identified that appears to have greater toxicity than the parent, **fipronil**. This **photodegradate** is not an animal metabolite and, while not present on corn, is potentially present on rice due to the foliar application.

Tolerances for residues of fipronil in/on corn and animal commodities have recently been established (40 CFR § 180.517). Fipronil is currently registered for use on commercial turf and pets in the U.S. Exposures from these uses will be considered in addition to rice when assessing aggregate exposure. In addition, a petition for establishment of temporary tolerances in/on cottonseed and cottonseed processing fractions (PP#5G04583) is currently in reject status pending receipt of revised Sections B and F and proposed tolerances for milk and eggs (CBTS No. 16288, DP Barcode D219819, G. Kramer, 11/12/96).

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

1. Identification of Active Ingredients

Chemical Name: [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile]

Common Name: Fipronil

PC Code Number: 129121

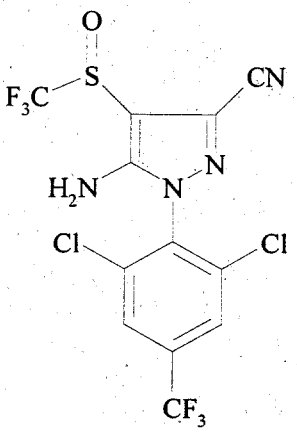
CAS Registry No.: 120068-37-3

Empirical Formula: $C_{12}H_4Cl_2F_6N_4$

Molecular Weight: 437.15

Structural Formulae (Fipronil and Metabolites):

Fipronil



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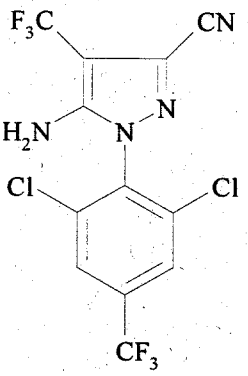

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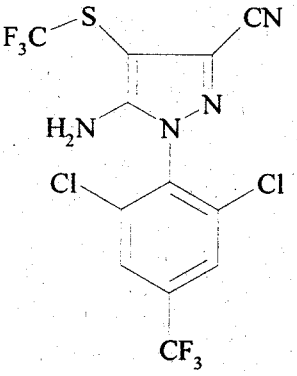

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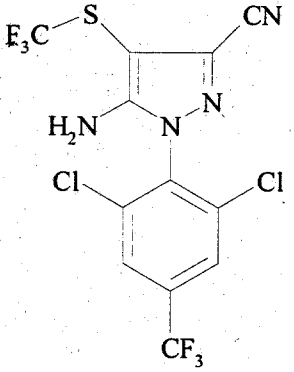

Physical and Chemical Properties for Fipronil	
Color	white
Physical State	powder
Odor	moldy odor at 23°C
Melting Point	195.5°-203°C
Boiling Point	N/A; TGAI is a solid
Density, Bulk Density, or Specific Gravity	1.6262 g/mL at 20°C

Physical and Chemical Properties for Fipronil	
Solubility	Solvent / Solubility deionized water 1.9 mg/L water, pH 5 0.0024 g/L water, pH 9 0.0022 g/L acetone 545.9 g/L 2-propanol 36.2 g/L dichloromethane 22.3 g/L ethyl acetate 264.9 g/L hexane 0.028 g/L methanol 137.5 g/L toluene 3.0 g/L octanol 12.2 g/L
Vapor Pressure	2.8×10^{-9} mm Hg at 20°C
Dissociation Constant	N/A
Octanol/Water Partition Coefficient	$P_{ow} = 10{,}154 \pm 1326$ (log $P_{ow} = 4.01$)
pH	5.90 - 6.10; 1% aqueous suspension with 2% acetonitrile at 23°C
Stability	slight decomposition (96.53%-93.79%) at 23°C in sunlight; stable at room temperature for 1 year, 35°C for 92 days, 52°C for 30 days, and 54°C for 14 days; Unstable in the presence of Fe ion
Flammability	N/A; TGAI is a solid
Viscosity	N/A; TGAI is a solid
Miscibility	N/A; TGAI is a solid

B. Human Risk Assessment

1. Hazard Assessment

See Table 1 for the requirements (CFR 158.135) for Food/Feed Use for **Fipronil** Technical.

Table 1

Test	Technical		Photodegradate
	Required	Satisfied	Acceptable studies
81-1 Acute Oral Toxicity	Y	Y	Y
81-2 Acute Dermal Toxicity	Y	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y	-
81-4 Primary Eye Irritation	Y	Y	-
81-5 Primary Dermal Irritation	Y	Y	-
81-6 Dermal Sensitization	Y	Y	-
81-7 Acute Delayed Neurotox. (Hen)	N	-	-
81-8-ss Acute Neurotox. Screening Battery (Rat)	Y	Y	N[3]
82-1 Oral Subchronic (Rodent)	Y	Y	Y
82-1 Oral Subchronic (Non-Rodent)	Y	Y	Y
82-2 21-Day Dermal	Y	Y	-
82-3 90-Day Dermal	N[1]	-	-
82-4 90-Day Inhalation	N[2]	-	-
82-5 90-Day Neurotoxicity (Hen)	N	-	-
82-5 90-Day Neurotoxicity (Mammal)	N	-	-
82-7 90 Day Neurotoxicity Screening Battery (Rat)	Y	Y	-
83-1 Chronic Toxicity (Rodent)	Y	Y	-
83-1 Chronic Toxicity (Non-rodent)	Y	Y	-
83-2 Oncogenicity (Rat)	Y	Y	-
83-2 Oncogenicity (Mouse)	Y	Y	-
83-3 Developmental Toxicity (Rodent)	Y	Y	Y
83-3 Developmental Toxicity(Non-rodent)	Y	Y	-
83-4 Reproduction	Y	Y	-
83-5 Chronic/Oncogenicity	Y	Y	-
83-6 Develop. Neurotoxicity Rat)	Y	Y	-
84-2 Mutagenicity—Gene Mutation, Bact.	Y	Y	Y
84-2 Mutagenicity—Gene Mutation, Mam.	Y	Y	Y
84-2 Mutagenicity—Struct. Chrom. Aber.	Y	Y	Y
84-4 Mutagenicity—Other Genotoxic Effects	N	N	-
85-1 General Metabolism	Y	Y	-
85-2 Dermal Penetration	Y	Y	Y
86-1 Domestic Animal Safety	N	-	-

Y yes, N no

[1] Not required based on low dermal toxicity observed in the 21-day dermal study, and based on expected exposure.

[2] Not required since significant exposure via inhalation not expected.

[3] This study needs positive control data to be submitted by the registrant.

a. Acute Toxicity

Adequacy of data base for acute toxicity (Series 81-1 to 81-6): The data base for acute toxicity for technical **fipronil** is considered complete. No additional studies are required at this time.

FIPRONIL PARENT - toxicity categories

§81-1 acute oral - MRID 42918628 , [II] - ♂ 92/♀ 103 mg/kg; ♂+♀ 97 mg/kg
§81-2 acute dermal - MRID 42918629, [III] - > 2000 mg/kg [rat]
§81-2 acute dermal - MRID 42918630, [II] - 354 mg/kg [rabbit]
§81-3 acute inhalation - MRID 4354440f, [II] - ♂ 0.36/♀ 0.42 mg/L; ♂+♀ 0.39 mg/L
§81-4 primary eye irritation - MRID 42918632, [III]
§81-5 primary dermal irritation - MRID 42918633, [IV]
§81-6 dermal sensitization - MRID 42918634, [non-sensitizing]

FIPRONIL FORMULATION Icon 6.2FS (Reg.: 264-LTT) - toxicity categories
data reviewed by Ian Blackwell, RD, 11/17/97)
§81-1 acute oral - MRID 4426192 , [II] - ♂ 217/♀396 mg/kg; ♂+♀275 mg/kg
§81-2 acute dermal - MRID 44261903, [III] - ♂ 802/♀ 865 mg/kg; ♂+♀ 841 mg/kg [rabbit]
§81-3 acute inhalation - MRID 44261904] - study unacceptable, **ASSUME CATEGORY I**
§81-4 primary eye irritation - MRID 44261905, [III]
§81-5 primary dermal irritation - MRID 44261906, [III]
§81-6 dermal sensitization - MRID not given, self validated **[SENSITIZER]**

FIPRONIL PHOTODEGRADATE (MB46513) - toxicity categories

§81-1 acute oral - MRID 43235401, [I] - ♂ 18/♀ 15 mg/kg
§81-2 acute dermal - MRID 43235402, [III] - > 2000 mg/kg [rat]
x§81-3 acute inhalation - no study
x§81-4 primary eye irritation - no study
§81-5 primary dermal irritation - no study
§81-6 dermal sensitization - no study

FIPRONIL METABOLITE (MB45897) - toxicity categories

§81-1 acute oral - MRID 44262819, [III] - ♂>2,000 mg/kg/♀>2,000 mg/kg
§81-2 acute dermal - MRID 44262820, [III] - > 2000 mg/kg [rat]

b. Subchronic Toxicity

Adequacy of data base for subchronic toxicity (Series 82): The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

I. Fipronil

82 1a Subchronic Oral Toxicity Feeding - Rat

Fipronil (95.4% a.i.) was administered in the diet to groups of ten male and ten female CD rats per group at dosages of 0, 1, 5, 30 or 300 ppm daily for thirteen weeks (MRID # 42918643). Overall mean body weight gain was decreased by 9% in the 300 ppm group females as compared to the controls. The 300 ppm group males and females had higher total protein concentrations than the controls in association with higher values for alpha-1, alpha-2 and beta globulins and lower albumin/globulin (A/G) ratios. The 5 and 30 ppm group males and females had similar alterations in protein values but the A/G ratios were not affected. At necropsy, the 300 ppm group males and females had higher absolute and relative thyroid weights. Absolute thyroid weights were increased in the 30 ppm group females. Absolute liver weights were increased in the 300 pm group males and in females which received 5 ppm or greater. Relative liver weights were increased in the 30 and 300 ppm group males and females. On histopathology, there was a significant increase in the incidence of hypertrophy of the follicular epithelium of the thyroid in the 300 ppm group males and females. Liver sections stained with Oil-Red-O showed a higher incidence and distribution of fat in the liver of the 300 ppm group males. **LOEL = 30 ppm for males (1.93 mg/kg/day) and**

females (2.28 mg/kg/day) based on alterations in serum protein values and increased weight of the liver and thyroid. NOEL = 5 ppm for males (0.33 mg/kg/day) and females (0.37 mg/kg/day).

Classification: Minimum

82-1a Subchronic Oral Toxicity Feeding - Mouse

In a subchronic toxicity study (MRID 44262804), **MB46030 (fipronil**; 95.4-96.5% a.i.) was administered to CD-1 albino mice (12/sex/dose) in the diet at nominal dose levels of 0, 1, 3, 10, or 25 ppm (13-week measured mean 0, 0.13, 0.38, 1.27, and 3.20 mg/kg/day, respectively, for males, and 0, 0.17, 0.57, 1.72, and 4.53 mg/kg/day, respectively, for females) for 13 weeks. Ophthalmoscopic examinations and blood and urine analyses were not conducted. Liver was the only tissue routinely examined histologically.

There were no deaths, clinical signs of toxicity or effects on food consumption. Male and female mice in the 25 ppm treatment group had mean body weight gains 2.3-3.2 g lower (22 and 34%, respectively) than the controls. Liver abnormalities were observed in all male treatment groups. Minimal to moderate liver cell periacinal hypertrophy with cytoplasmic vacuolation was present in 0/12, 2/12, 3/12, 6/12 and 10/12 rats from controls to high dose group. There was one 10 ppm male with a grossly enlarged liver. Absolute and relative liver weights were increased 23 and 33 % above controls, respectively at 25 ppm. Females did not exhibit a similar response to treatment. One female in the 25 ppm group and two in the 10 ppm group exhibited slight midzonal hepatocytic fatty vacuolation, and mean relative liver weights for both groups were 8-13% higher than the controls. The above treatment induced changes are considered adaptive rather than toxic. No neoplastic tissue was observed. **The LOEL was 25 ppm (3.2 and 4.53 mg/kg/day, for males and females, respectively) based on a possible decreased body weight gain. The NOAEL was 10 ppm (1.27 and 1.72 mg/kg/day, for males and females, respectively). The NOEL is less than or equal to 1 ppm (0.13 and 0.17 mg/kg/day for males and females, respectively) based on hepatic hypertrophy at all doses (this change is considered adaptive rather than adverse).**

This 90-day subchronic toxicity study (dietary) is classified **acceptable (non-guideline)** due to its abbreviated protocol and its designed as a range finding study and does not satisfies the Subdivision F guideline requirement for a subchronic toxicity study in rodents (§82-1a).

82-1b Subchronic Oral Toxicity [capsule] - Dog

Fipronil (95.4% a.i.) was administered in capsules to groups of four male and four female beagle dogs per group at dosages of 0, 0.5, 2.0 or 10.0 mg/kg/day for 13 weeks (MRID # 42918642). One male and three females in the 10 mg/kg/day group were euthanized during the second week of treatment due to poor condition.

Extensive clinical signs of toxicity, including those involving the nervous system, were also seen in the surviving animals in this group. The only clinical sign of toxicity in the 2.0 mg/kg/day group was inappetence in two of four females. Abnormal findings in the routine physical and neurological examinations during the course of the study were confined to the 10.0 mg/kg/day group. Mean body weight gain over the course of the study was decreased in females in the 2.0 and 10.0 mg/kg/day groups by 17% and 12%, respectively, in comparison to the controls. (Mean values for females in the 10.0 mg/kg/day group were based on only one animal after Day 14.) No other treatment-related findings were reported. **LOEL = 10.0 mg/kg/day for males (based on clinical signs of toxicity) and 2.0 mg/kg/day for females (based on clinical signs of toxicity and decreased body weight gain). NOEL = 2.0 mg/kg/day for males and 0.5 mg/kg/day for females.**

Classification: Guideline

82-2 Repeated Dose Dermal – Rat

M&B 460430 (96.7% a.i.) was applied in a 0.5% solution of carboxymethylcellulose to the intact skin of 6 New Zealand White rabbits/sex/group at doses of 0, 0.5, 1.0, 5.0 or 10.0 mg/kg/day for six hours per day for 15 doses

over a 21-day period (MRID # 42918644). Males and females in the 10 mg/kg/day group had decreased mean body weight gain and food consumption in comparison to the control group. One male and one female in the 10 mg/kg/day group exhibited signs of extreme hyperactivity that may have been treatment-related. **Systemic LOEL = 10 mg/kg/day based on decreased body weight gain and food consumption; Dermal irritation LOEL > 10.0 mg/kg/day. Systemic NOEL = 5.0 mg/kg/day; Dermal irritation NOEL ≥ 10.0 mg/kg/day.**

Classification: Guideline

ii. MB 46513

82 1a Subchronic Oral Toxicity Feeding - Rat

In this subchronic rat study (MRID # 43559501), MB 46513 was administered in the diet to groups of ten male and ten female CD rats at dosages of 0, 0.5, 3, 10 or 30 ppm (males: 0, 0.029, 0.177, 0.594 and 1.772 mg/kg/day; females: 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day, respectively) daily for 90 days.

There were four deaths in both sexes of the 30 ppm group during the treatment period. There was an increased incidence of clinical signs of neurotoxicity (aggressivity, irritability to touch, increased motor activity and curling up on handling) in the 10 and 30 ppm group males and females. One male in the 3 ppm group was also observed to display most of these signs. Mean body weights were statistically decreased in the 30 ppm group males and females and the 10 ppm group males at multiple weekly measurements during the study. Overall mean body weight gains for the 10 and 30 ppm group males was decreased 15.4 and 12.9, respectively. Mean weekly food consumption and food conversion efficiency for the 30 ppm group males and females were lower than the controls during the first two weeks of the study only. There were no treatment-related changes in hematology or urinalysis parameters. Alterations in clinical chemistry parameters were of no toxicological significance. Treatment-related decreases were seen in T_4 at weeks 2 and 10 in the 30 ppm group males and in the 30 ppm group females at week 10. There was also a decrease in T_3 in the 30 ppm group males at week 10. However, there were no changes in TSH, or the thyroid gland on macroscopic or microscopic examination. Therefore, the toxicological significance of the hormone alterations is questionable. There were no treatment-related macroscopic or microscopic necropsy changes. **The study demonstrates that the metabolite is more toxic than the parent chemical (MB 46030) when administered to rats for 90 days. The Lowest Observed Effect Level (LOEL) was 3 ppm (0.177 and 0.210 mg/kg/day for males and females, respectively) based on the occurrence of agressivity, irritability to touch and increased motor activity in one male (these signs are also observed in the mouse). The No Observed Effect Level (NOEL) was 0.5 ppm (0.029 and 0.035 mg/kg/day for males and females, respectively).**

This study is classified as **Acceptable** and **satisfies** the data requirements for a subchronic rat study (82-1).

82-1a Subchronic Oral Toxicity Feeding - Mouse

In a subchronic toxicity study (MRID 44262811), **MB46513** (a **photodegradate** of fipronil; 96% a.i.) was administered to OF1 mice (10/sex/dose) in the diet at nominal dose levels of 0, 0.5, 2, or 10 ppm (13-week measured mean 0, 0.08, 0.32 or 1.74 mg/kg/day for males; 0, 0.11, 0.43, or 2.15 mg/kg/day for females) for 13 weeks.

In the 10 ppm treatment group, 9/10 males died prematurely (between days 20 and 62) and 1/10 was sacrificed moribund (day 84); 1/10 females died on day 5. On one occasion each, two of the males exhibited excessive jumps, and on several occasions one male exhibited aggressiveness and/or irritability. Diffuse centrilobular hypertrophy of the liver was noted in 6/10 males. The severity of the condition was described as mild in the five males that died prematurely and moderate in the one male that was sacrificed. The liver of the sacrificed animal also had moderate multifocal mitotic figures and mild multifocal extramedullary hematopoiesis. In addition, three males had enlarged livers and four had atrophied thymus glands. The organs of males in the 10 ppm treatment group were not weighed. The organs of females in the 10 ppm treatment group appeared normal. In the 2 ppm treatment group, two males on two occasions each exhibited aggressive and irritable behavior with increased motor activity in one of them.

Although 1 male and 1 female in the 0.5 ppm treatment group exhibited aggressive behavior (total of four occasions) this could not be definitively attributed to treatment because; 1) low frequency, 2) only one sign; 3) no effect in females at any higher dose. No differences in organ weights or gross or microscopic pathology were observed between mice in the 2 or 0.5 ppm treatment groups and the controls. Body weights, food consumption, and clinical blood chemistry were not affected in any treatment group. No neoplastic tissue was observed in mice in the treatment and control groups. Hematology, ophthalmoscopic and urine analyses were not conducted during the study. **The LOEL for this study is 2 ppm (0.32 mg/kg/day), based on the aggressive and irritable behavior with increased motor activity in males. The NOEL is 0.5 ppm (0.08 mg/kg/day).**

This 90-day subchronic toxicity study (dietary) is classified **acceptable** and satisfies the Subdivision F guideline requirement for a subchronic toxicity study in rodents (§82-1a).

82-1a Subchronic Oral Toxicity Feeding - Dog

In a subchronic toxicity study (MRID 44262812 - main; 44262810 - range-finding), **MB46513** (96.0% a.i.), a **photodegradate** of fipronil, was administered to 5 beagle dogs/sex/dose by feeding at dose levels of 0, 3.5, 9.5, or 35 ppm (mean achieved dosages of 0, 0.10, 0.27, or 0.95 mg/kg/day for males and 0, 0.10, 0.29, or 1.05 mg/kg/day for females) for 90 days. In a range finding study, 2 dogs/sex/dose (0, 27, 80, or 270 ppm) were treated with MB 46513 for 28 days.

In the **28 day range finding study** ½ males at 27 ppm (1 mg/kg/day) had convulsions at 28 days and animals at 80 ppm had clinical signs as early as day 4 (this group had to be sacrificed early due to extreme toxicity). In the **main study**, 35 ppm group, 1/5 females was sacrificed prematurely after exhibiting increase salivation, prostration, writhing, tremors, absence of rotular reflex, noisy breathing, and dyspnea. Histopathological examination of this female after 28 days revealed multifocal myocardial necrosis associated with intramural coronary arteritis. Behavioral changes were observed in a second female in the 35 ppm treatment group consisting of excessive barking and aggressivity on one occasion and irritability, tremors, and increased salivation on another occasion. No other treatment-related behavioral effects were observed in the 35 ppm treatment group. No treatment-related behavior effects were observed in any dogs in the 9.5 or 3.5 ppm treatment groups. No treatment-related differences in ophthalmology, hematology, clinical blood chemistry or urinalysis parameters or gross pathology were observed between dogs in any treatment group and the controls. No neoplastic tissue was observed in any of the treatment groups. **The LOEL is 35 ppm (1.05 mg/kg/day), based on behavioral changes in 2/5 females. The NOEL is 9.5 ppm (0.29 mg/kg/day).**

This subchronic toxicity study is classified **acceptable** and satisfies the guideline requirements for a subchronic oral study (**§82-1b**) in non-rodents.

c. Chronic Toxicity

Adequacy of data base for chronic toxicity (Series 83-1, 83-5): The data base for chronic toxicity is considered complete. No additional studies are required at this time.

83-1a Chronic Feeding – Rat

Fifteen (15) CD rats/sex/group were administered **fipronil** (95.4%) in the diet for 52 weeks to assess the chronic toxicity of the chemical (MRID # 42918648). An additional 15 rats/sex/group were fed the chemical for 52 weeks and then were untreated for an additional 13 weeks to test the reversibility of treatment-related changes. Fifty rats/sex/group were supposed to be treated for 104 weeks to assess the carcinogenic potential of the chemical. The doses administered in all the phases were 0, 0.5, 1.5, 30 and 300 ppm. The carcinogenic phase of the study was terminated after 89 and 91 weeks in males and females, respectively, due to excessive mortality and to ensure that a sufficient number of animals were available for the terminal sacrifices. No treatment related differences in mortality between the groups were observed.

Evidence of treatment-related toxicity included: 1) neurotoxicity (including seizures which resulted in death) in the 1.5, 30 and 300 ppm group males and females; 2) decreased body weight gain in the 300 ppm group males and females and the 30 ppm group females; 3) decreased food consumption and food conversion efficiency in the 300 ppm group males and females at the beginning of the study; 4) decreased hematology parameters in the 300 ppm group males and females in comparison to the control groups (values were comparable to pretreatment measures); 5) alterations in clinical chemistry (increased cholesterol and calcium values; protein alterations with increased total protein, decreased albumin and increased globulins) mostly in the 30 and 300 ppm group males and females; protein alterations were seen in the 1.5 ppm group males after 76 and 81 weeks of treatment; 6) alterations in thyroid hormones (increased TSH and decreased T_4 levels) in all treated groups at some time points with the 30 and 300 ppm group males and females consistently affected; 7) alterations in urinalysis parameters (lower pH, higher protein, elevated urine volume with decreased specific gravity) in the 30 and 300 ppm groups (predominately males); 8) changes on gross necropsy (large and/or pale kidneys and large livers, adrenals and thyroids) in the 30 and 300 ppm group males and females; 9) increased absolute and relative weights of the liver and thyroids in the 30 and 300 ppm group males and females; 10) increased incidence and severity of progressive senile nephropathy in the 30 and 300 ppm group males and females. **LOEL = 1.5 ppm for males (0.059 mg/kg/day) and females (0.078 mg/kg/day) based on an increased incidence of clinical signs and alterations in clinical chemistry and thyroid parameters. NOEL = 0.5 ppm for males (0.019 mg/kg/day) and females (0.025 mg/kg/day).**

Benign (follicular cell adenoma) and malignant (follicular cell carcinoma) neoplastic changes were observed in the thyroid gland in increased incidences in all the treated animals as compared to the control group. However, only the 300 ppm group males and females exceeded the historical incidence of these tumors, either alone or in combination, for this strain of rat in this laboratory. **The study demonstrated that fipronil is carcinogenic to rats at doses of 300 ppm in males (12.68 mg/kg/day) and females (16.75 mg/kg/day).**

Classification: Minimum

83-1b Chronic Oral Toxicity [capsule] - Dog

Male and female beagle dogs were administered **fipronil** (96.8% a.i.) in capsules at dosages of 0, 0.2, 2.0 or 5.0 mg/kg/day for 52 weeks (MRID # 42918645).

One male in the 2.0 mg/kg/day group and two males in the 5.0 mg/kg/day group were sacrificed during the study due to poor condition. Clinical signs of neurotoxicity were seen in the 2.0 and 5.0 mg/kg/day groups beginning in Week 2. Abnormal neurological examinations were observed in males and females in the 5.0 mg/kg/day group and in females in the 2.0 mg/kg/day group. Body weight gain was decreased in the 5.0 mg/kg/day group females, however the mean decrease was due to reduced gain in one female.
LOEL = 2.0 mg/kg day based on clinical signs of neurotoxicity and abnormal neurological examinations. NOEL = 0.2 mg/kg/day.

Classification: Guideline

d. Carcinogenicity

Adequacy of data base for Carcinogenicity (Series 83-2, 83-5): The data base for carcinogenicity is considered complete. No additional studies are required at this time.

8 3 -2a Carcinogenicity Study - rat

This study (MRID 42918648) is presented in the Chronic Toxicity Section. see 83-5 above.

83-2b Carcinogenicity [feeding] - Mouse

Six groups of 20 male and 20 female CD-1 mice/group were administered **fipronil** (95.4% a.i.) in the diet at dosages of either 0, 0.1, 0.5, 10, 30 or 60 ppm for 52 weeks to test the chronic toxicity of the chemical (MRID #

42918649). An additional six groups of 52 male and 52 female mice were treated at the same dosages of 78 weeks to test the carcinogenic potential of the chemical. Due to excessive mortality, animals in the 60 ppm group were sacrificed during Week 10 of the study.

Signs of toxicity in the remaining groups included: 1) decreased body weight gain in the 30 ppm group males and females at most of the evaluation periods; values for the 10 ppm group were also decreased, although not as consistently; 2) decreased food consumption in the 30 ppm group females; 3) decreased food conversion efficiency in the 10 and 30 ppm group males; 4) altered white blood cell differential counts in the 30 ppm group females; 5) increased incidence of liver pathology on gross examination in the 30 ppm group males in the carcinogenicity phase; 6) increased absolute and/or relative liver weights in the 10 and 30 ppm group males and females in both the toxicity and carcinogenicity phases; 7) increased incidence of periacinal and microvesicular vacuolation in the liver of the 10 and 30 ppm group males at the toxicity and carcinogenicity phase necropsies; 8) increased incidence of hepatocellular hyperplasia and chronic degenerative changes in the liver of the 30 ppm group males which died or were sacrificed during the treatment period of the carcinogenicity phase. There was an increased incidence of malignant hepatocellular tumors in males in the 30 ppm group as compared to the controls at the carcinogenicity phase necropsy. However, the incidence in the control group was lower than the historical incidence with this species and this laboratory. In addition, the difference in incidence was not statistically significant, and when benign and malignant tumors were considered together, the incidences were similar. **LOEL = 10 ppm (1.181 mg/kg/day for males and 1.230 mg/kg/day for females) based on decreased body weight gain, decreased food conversion efficiency (males), increased liver weights and increased incidence of hepatic histopathological changes. NOEL = 0.5 ppm (0.055 mg/kg/day for males and 0.063 mg/kg/day for females).**

The study demonstrated that Fipronil is not carcinogenic to CD-1 mice when administered at doses of 30 ppm.

Classification: Minimum

e. Developmental Toxicity

Adequacy of data base for Developmental Toxicity (Series 83-3): The data base for developmental toxicity is considered complete. No additional studies are required at this time.

I. Fipronil

83-3a Prenatal Developmental Study - Rat

Specific Pathogen Free female rats of the Crl:CD^{R} (SD) BR VAF/Plus strain from Charles River, St. Aubin les Elbeuf, France, received either 0, 1, 4, or 20 mg/kg/day **fipronil** (93% a.i.) by oral gavage from gestation days 6 through 15, inclusive (MRID # 429779-03).

Maternal toxicity was noted at 20 mg/kg/day in the form of reduced body weight gain during the dosing period (82.6% of control, gestation days 6-16) and to a lesser extent for the period including the dosing plus post dosing period (90.1% of control, gestation days 6 though 20) and for the entire gestation period (91.8% of control, gestation days 2 through 20). There was an increase in water consumption in the high dose group throughout the study ranging from a 3 to 28% increase as compared to control; there was an 18% increase over control in the high dose group for gestation days 6-15. Food consumption was slightly decreased in the high dose group at the beginning of the dosing period (days 6-11) with an overall reduction of 90% of control for gestation days 6-15, after which no treatment-related effect was noted. There was a slight reduction in the high dose group food efficiency during the dosing period, 27.8, 28.5, 27.0 and 25.3% for the control, low, mid and high dose groups, respectively. No effects were noted in developmental toxicity parameters.

Maternal toxicity LOEL = 20 mg/kg/day based on reduced body weight gain, increased water consumption, reduced food consumption and reduced food efficiency. Maternal toxicity NOEL = 4 mg/kg/day.

Developmental toxicity LOEL = greater than 20 mg/kg/day. Developmental toxicity NOEL = 20 mg/kg/day or higher.

Classification: Minimum

83-3b Prenatal Developmental Study - Rabbit

Sexually mature virgin female New Zealand White rabbits from Ranch Rabbits, Crawley Down, Sussex, England, received either 0, 0.1, 0.2, 0.5 or 1.0 mg/kg/day **fipronil** (95.4% a.i.) by oral gavage from gestation days 6 through 19, inclusive (MRID # 42918646).

Maternal toxicity was noted at all dose levels tested in the form of reduced body weight gain at all gestation day periods evaluated. Body weight gains for the treatment period (gestation days 6-20) were 73, 73, 50 and 30% of control for the 0.1, 0.2, 0.5 and 1.0 mg/kg/day groups, respectively. For gestation days 20-28, weight gains of the treated animals exceeded the controls. For gestation days 0-28, gains were 88, 86, 81 and 67% of control for the 0.1, 0.2, 0.5 and 1.0 mg/kg/day groups. All treated groups consumed less food than that of the control group during the dosing period; the differences were statistically significant for the two highest dose groups. Food efficiency was decreased in all treated groups. No effects were noted in developmental toxicity parameters.

Maternal toxicity LOEL ≤ 0.1 mg/kg/day based on reduced body weight gain, reduced food consumption and efficiency. Maternal toxicity NOEL is < 0.1 mg/kg/day.

Developmental toxicity LOEL > 1.0 mg/kg/day. Developmental toxicity NOEL ≥ 1.0 mg/kg/day.

Classification: Minimum

ii. MB 46513

83-3a Prenatal Developmental Study - Rat

In a developmental toxicity (teratology) study (MRID# 44275001), adult virgin female rats (CD strain, Sprague Dawley Crl: CD (SD) BR from Charles River Laboratories, St Aubin les Elbeuf, France) received either 0, 0.5, 1.0, or 2.5 mg/kg/day of MB 046513 (Purity: 992 g/kg, Batch 805 DAP/DA999) suspended (w/v) in an aqueous solution of methylcellulose 400 (Fluka, Mulhouse, France) at 0.5% by oral gavage from gestation days 6 to 15 inclusive of presumed gestation. Maternal parameters included clinical signs of toxicity, body weights (on gestation day 0, daily from gestation day 6-16 and on gestation day 20) and food consumption (interval gestation day 0-6, daily from gestation days 6-15 and the interval of gestation day 16- 20). All surviving animals were sacrificed on gestation day 20 and each female was subjected to macroscopic examination of the visceral organs, the reproductive tract was weighed (gravid uterine weight), dissected out and the number of corpora lutea in each ovary, the number of implantation sites, number and localization of resorption sites (classified as early and late), the number and distribution of live and dead foetuses in each uterine horn were determined along with the sex of viable fetuses and the individual weights of viable fetuses and placenta were measured. The viable fetuses were sacrificed, subjected to an external examination and the approximately half of the viable fetuses from each litter were prepared for soft tissue examination and the remaining for skeletal examination.

Maternal toxicity was noted as clinical signs in the high dose animals as hair loss on either the paws, limbs, flanks, abdomen and/or thorax. The high dose group had lower body weight gains on study days 6-16 (58.1% of control), study days 0-20 (90.0% of control), study days 6-20 (83.9% of control) and days 0-20 corrected for gravid uterine weights (78.3% of control). The high dose group also consumed less food during the dosing period and there was lower food efficiency relative to the control group except for the post dosing period where an increase was noted which is indicative of a rebound relative to toxicity. **The Maternal Toxicity LOEL was 2.5 mg/kg/day and the NOEL was 1.0 mg/kg/day based an increase in clinical signs of toxicity on reduced body weight gain, food consumption and food efficiency.**

Developmental toxicity was noted as a very slight increase in the fetal and litter incidence of incomplete or reduced ossification in several bones in the high dose group, including the hyoid body, 5th/6th sternebrae, 1st thoracic body, pubic bone and 1 or 2 metatarsi. There was also a slight reduction in fetal body weight (males 97.5% of control, females 97.7% of control) in the high dose group, although statistically significant, the changes are too small to be biologically relevant. **The Developmental Toxicity LOEL was 2.5 mg/kg/day and the NOEL was 1.0 mg/kg/day based on the slight increase in fetal and litter incidence of reduced ossification of several bones.**

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§ 83-3a) for a teratology study in rats.

f. Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity (Series 83-4: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

83-4 Two-Generation Reproduction Study - Rat

Thirty CD rats/sex/group received **fipronil** (95.4% a.i.) continuously in the diet at concentrations of 0, 3, 30 and 300 ppm (equivalent to 0, 0.25, 2.54 and 26.03 and 0.27, 2.74 and 28.40 mg/kg/day for males and females, respectively) (MRID # 42918647). Parental (systemic) toxicity was noted in the form of the following: 1) increased mortality in the 300 ppm group males and females in the F_0 and F_1 generations; 2) decreased body weight gain pre-mating in the 300 ppm group males and females in the F_0 and F_1 generations and in the 300 ppm group females during gestation and lactation in the F_0 generation; 3) food consumption in the 300 ppm group males and females during pre-mating in the F_0 generation; 4) increase in the absolute and relative weights of the thyroid glands and liver in the 30 and 300 ppm group males and females of the F_0 and F_1 generations; decrease in the absolute and relative weights of the ovaries in the 300 ppm group females in the F_0 generation; decrease in the absolute weight of the pituitary gland in the 30 and 300 ppm group females and decrease in the relative weight in all the treated female groups in the F_1 parental animals; decrease in the absolute and relative weights of the testes in the 300 ppm group males in the F_1 parental animals; 5) increased incidence of centriacinar fatty vacuolation in the livers of the 300 ppm group females in both the F_0 and F_1 generations; and 6) increased incidence of follicular epithelial hypertrophy of the thyroid glands in the 300 ppm group males and females in the F_0 generation and in the 30 and 300 ppm group females in the F_1 generation.

Reproductive toxicity was noted in the form of the following findings in the 300 ppm group: 1) clinical signs of toxicity in the F_1 and F_2 offspring; 2) decreased litter size in the F_1 and F_2 litters; 3) decreased body weights in the F_1 and F_2 litters; 4) decrease in the percentage of F_1 parental animals mating; 5) reduction in fertility index in F_1 parental animals; 6) reduced post-implantation survival and offspring postnatal survivability in the F_2 litters; and 7) delay in physical development in the 300 ppm group of the F_1 and F_2 litters.

The Lowest Observed Effect Level (LOEL) for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on increased weight of the thyroid glands and liver in males and females; decreased weight of the pituitary gland in females; and an increased incidence of follicular epithelial hypertrophy in the females. The No Observed Effect Level (NOEL) for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females).

The LOEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females) based on clinical signs of toxicity in the F_1 and F_2 offspring; decreased litter size in the F_1 and F_2 litters; decreased body weights in the F_1 and F_2 litters; decrease in the percentage of F_1 parental animals mating; reduction in fertility index in F_1 parental animals; reduced post-implantation survival and offspring postnatal survivability in the F_2 litters; and delay in physical development in the F_1 and F_2 offspring. The NOEL for reproductive toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females).

Classification: Minimum

g. Neurotoxicity

Adequacy of data base for Neurotoxicity (Series 81-8, 82-7, 83-6):

i. Fipronil

81-8 Acute Neurotoxicity - Rat

A single dose of **fipronil** (96.7% a.i.) in corn oil was administered by gavage to four groups of 15 CD rats/sex/group at dosages of either 0, 0.5, 5.0 or 50.0 mg/kg.

Five males and one female in the 50 mg/kg group died during the study (MRID # 42918635). Treatment-related clinical signs of toxicity, including neurotoxicity, were seen with the 50 mg/kg group animals, especially the males. Males in the 50 mg/kg group had decreased body weights in comparison to the controls. During the open field evaluations of the functional observational battery (at 7 hours, 7 days and 14 days post-treatment), effects of both stimulation and depression of the nervous system were seen. Those parameters for which there were statistically significant changes in males included gait, fine tremors (females also), coarse tremors, urination, mean number of rears (females also), approach response, pupil size, muscle tone (females also), air righting and mean hind leg splay (females also). Mean rectal body temperature was also decreased in the males and females of this group. The only treatment-related effects in the 5.0 mg/kg group at this time point were decreased mean body temperature in males and decreased mean hind leg splay in males and females. On Days 7 and 14, the effects were minor in comparison, but females in the 50 mg/kg group had a statistically significant increase in hind leg splay at both evaluations. Mean motor activity was decreased by 90 and 93% in the 50 mg/kg group males and females, respectively, at the 8-hour evaluation. At Day 7, significant increases in mean activity for the 0.5 and 5.0 mg/kg group males were observed. However, supplemental statistical analysis demonstrated that the test substance did not alter motor activity when compared with pretreatment activity. There were no significant differences between the treated and control groups at Day 14. There were no treatment-related gross or microscopic changes on post-mortem examination of the central and peripheral nervous systems. **The No Observed Effect Level (NOEL) = 0.5 mg/kg for males and females. The Low Observed Effect Level (LOEL) = 5.0 mg/kg for males and females based on decreased hind leg splay at the 7 hour post-treatment evaluation in males and females.**

Classification: Minimum

82-7 Subchronic neurotoxicity Screening Battery - rat

In this subchronic neurotoxicity study, male and female Sprague-Dawley rats (15/sex/dose) were fed test diets containing M&B 46030 at 0 (basal diet), 0.5, 5.0, or 150 ppm (equivalent to 0, 0.0297, 0.301, or 8.89 mg/kg/day, males; 0, 0.0354, 0.351 or 10.8 mg/kg/day, females) (MRID No. 43291703). Neurobehavioral screening, consisting of Functional Observational Battery and motor activity evaluations, was performed at pretreatment, and during Weeks 4, 9 and 13. At terminal sacrifice, six animals/sex/dose were anesthetized and perfusion fixed *in situ* for neuropathological evaluation. With the exception of one low-dose female which was found dead on Day 16, all remaining animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Decreases in mean body weight, observed in high-dose males and females at Week 1 of treatment, were judged to be slight (6.5%, males; 6.9%, females). The decrease in body weight was accompanied by a concomitant decrease in food consumption, which would suggest a palatability problem, rather than a treatment-related effect. FOB findings revealed minimal effects in high-dose animals at the Weeks 4, 9 and 13 evaluations. High-dose males had a decreased incidence of no urination and an increased incidence of exaggerated tail pinch response. High-dose males and females had an increased incidence startle responses in the manipulative observations. High-dose females had increased forelimb grip strength at Week 13. The mean body weights of treated males were significantly greater than the concurrent control values. Necropsy findings did not reveal any treatment-related gross pathological or histopathological findings. Although histopathological lesions were observed, incidences were low and attributed by the study pathologist to animal variation and artifactual changes. **Based on the results (FOB findings) of this study, the LOEL was established at 150 ppm (8.89 mg/kg/day, males; 10.8 mg/kg/day, females); the NOEL was established at 5.0 ppm (0.301 mg/kg/day, males; 0.351 mg/kg/day, females).**

This study is classified as **Core - Acceptable** and satisfies guideline requirements (§82-7) for a subchronic neurotoxicity screening battery in the rat.

83-6 Developmental Neurotoxicity - Rat

Fipronil (96.1% a.i.) was administered to 30 female Sprague-Dawley rats/group in the diet at dose levels of 0, 0.5, 10 or 200 ppm (0.05, 0.90 or 15 mg/kg/day, respectively) from Gestation Day 6 to Lactation Day 10 (MRID # 44039002).

There was no evidence of a treatment-related effect on maternal survival or clinical signs of toxicity. Two females in the 200 ppm group died during lactation, but there was no evidence that the deaths were treatment-related. Mean maternal body weight values for the 200 ppm group were reduced 15.5%, 10.0% and 8.6% in comparison to the controls on Gestation Days 10, 15 and 20, respectively. Mean body weight gain was statistically decreased for Gestation Day interval 6-10, but increased for interval 10-15. Statistically significant reductions in mean body weight were seen in the 200 ppm group on Lactation Days 0 and 4. Mean body weight gain was statistically increased on Lactation Days 4-11. A statistically significant reduction in group mean food consumption was noted in the 200 ppm group for Gestation Days 6 to 10 but was comparable to the controls for other intervals.

Pregnancy rate and gestation length for treated animals were comparable to the control group. There was no evidence of a treatment-related effect on gross necropsy findings. **The maternal LOEL is 200 ppm (15 mg/kg/day), based on decreased body weight, body weight gain and food consumption. The maternal NOEL was 10 ppm (0.90 mg/kg/day).**

At 200 ppm, litter size was not affected by treatment, but the live birth index was decreased (not statistically significant). The pup viability index (survival from Postnatal Days 0-4) for the 200 ppm group was significantly decreased (98.9% for control vs. 75.5% for 200 ppm group). The weaning index (survival from Postnatal Days 4-21) was decreased for this group, but the difference was not statistically significant. Pup sex distribution was not affected. There was a statistically significant decrease in group mean body weights of both male and female offspring at all recorded intervals during lactation (9.2-34.1% and 8.1-33.8% decrease in males and females, respectively) and for various periods post-weaning. Statistically significant increases in the mean day of achieving pinna detachment, upper and lower incisor eruption, vaginal patency and preputial separation were noted. Auditory startle testing on Postnatal Day 22 demonstrated a statistically significant decrease in the maximum response for males and females. There was no significant difference in the time to maximum response or average response. There were no changes in this parameter on Postnatal Day 60. Motor activity testing on Postnatal Day 17 showed statistically significant increases in motor activity counts for females. Swimming direction scores on Day 6 were reduced for the males and females, although only the males were statistically significant. On Day 14, the scores were comparable. Water "Y" maze time trials for learning and memory showed a statistically significant increase in time required to complete the maze for females in Trials 5 and 6 on Day 24. There were no statistically significant differences for either sex on Days 25, 30, 60, 61 or 65. Statistically significant decreases in absolute brain weights for both sexes, compared to control values, were found on Postnatal Days 11 (20% and 11% decrease in males and females, respectively) and 60 (≈ 7% decrease in males and females). Terminal body weights were also decreased for this group on these days. On Day 11, the relative brain weights for both sexes were significantly increased in comparison to the controls. On Day 60, the values for the control and 200 ppm groups were comparable. There was no evidence of a treatment-related effect on the gross macroscopic or microscopic examinations (including the central and peripheral nervous systems) of the pups sacrificed on Postnatal Days 11 and 60. *At 10 ppm*, group mean weights were significantly reduced for females at all recorded intervals and for males on Days 4 and 17. Post-weaning weights were not affected. There was a statistically significant increase in the time of preputial separation in the 10 ppm group males. Females had a statistically significant increase in mean motor activity counts on Postnatal Day 17. **The developmental LOEL is 10 ppm (0.9 mg/kg/day), based on statistically significant decrease in group mean pup weights during lactation and significant increase in time of preputial separation in males. The developmental neurotoxicity LOEL is 10 ppm (0.9 mg/kg/day) based on a significant increase in mean motor activity counts in females on Postnatal Day 17. The NOEL for developmental and developmental neurotoxicity is 0.5 ppm (0.05 mg/kg/day). It is noted that developmental neurotoxicity**

occurred in the absence of maternal toxicity in this study.

Classification: Acceptable (Guideline)

ii. MB 46513

81-8 Acute Neurotoxicity - Rat

In an acute neurotoxicity study (MRID 44262808), **MB46513, a photometabolite** of fipronil (99.5% a.i.), was administered in corn oil by oral intubation to Crl:CD BR rats (12/sex/dose) at dose levels of 0, 0.5, 2, or 12 mg/kg. The rats were evaluated for reactions in functional observations and motor activity measurements at 6 hours, 7 days, and 14 days post dosing. Clinical signs, body weights, and food consumption were monitored. At study termination, brains were weighed and measured, and neural tissues were processed for microscopic evaluation.

No animals died and there were no treatment-related clinical signs of toxicity. At 12 mg/kg, significant decreases in body weight gains and food consumption were noted for the high-dose males and females during the week following treatment. By the second week, both had returned to the control levels. Body weight gains and food consumption for the low- and mid-dose groups and mean body weights for all treated groups were not significantly different from the controls throughout the study. Food efficiency was not affected by treatment. Behavioral responses were also affected by treatment with MB46513 at 12 mg/kg. At the estimated peak response time, 6 hours post dosing, significant decreases in locomotor activity during the first 30 minutes of observation were noted among high-dose males and females. There were no significant differences in any dose group on days 7 and 14. Treatment-related decreases in hindlimb splay and rectal temperature at 6 hours post dose were observed in high-dose males and females. In addition, decreases in the proportion of high-dose males with an immediate righting reflex on days 7 and 14 were possibly treatment related. Decreased forelimb grip strength in high-dose males on day 7 and increased forelimb grip strength in high-dose females at 6 hours post dosing was possibly related to the treatment, because there were also slight increases in forelimb grip strength in high-dose males at 6 hours and slight decreases in forelimb grip strength in high dose females at 7 days and in high-dose males and females at 14 days. There were no significant differences among groups in neuropathology. **Based on these findings, the neurobehavioral LOEL for rats is 12 mg/kg. The NOEL is 2 mg/kg.**

This study is classified **unacceptable** and does not satisfy the guideline requirement for an acute neurotoxicity study in rodents **(§81-8)**. The study may be upgraded after receipt and favorable review of positive control data for the performing laboratory.

h. Mutagenicity

Adequacy of data base for Mutagenicity (Series 84): The available studies indicate that **fipronil** and the fipronil **photodegradate, MB46513** are not mutagenic in bacteria and are not clastogenic in vitro or in vivo up to doses that showed clear test material interaction with the target cells.. Based on these considerations, the Committee concluded that there is no concern for mutagenicity.

The submitted test battery for both compounds satisfy the new mutagenicity initial testing battery guidelines. No further studies are required at this time. The data base for Mutagenicity is considered adequate. Based on the available mutagenicity studies, there are no concerns for mutagenicity at this time.

STUDY TYPE REFERENCE	CONCLUSIONS
FIPRONIL	
Gene Mutation/bacteria *Salmonella typhimurium* (MRID # 42918652)	**Fipronil** (90.6% a.i.) was not mutagenic Classification: Acceptable
Gene Mutation/*In vitro* assay in mammalian cells Chinese hamster V79 cells (MRID # 42918651)	**Fipronil** (97.2% a.i.) was negative for inducing forward gene mutations at the HGPRT locus in cultured Chinese hamster V79 cells. Classification: Acceptable
Cytogenetics/Human lymphocytes (MRID # 42918653)	There was no evidence of a clastogenic effect when human lymphocytes were exposed *in vitro* to **fipronil** (90.6% a.i.) Classification: Acceptable
Cytogenetics *In vivo* mouse micronucleus assay (MRID # 43680801)	There was no evidence of a clastogenic or aneugenic effect at any **MB 460030** (96.2%) dose or at any harvest time. Classification: Acceptable
MB 46513 (photodegradate)	
Gene Mutation/bacteria *Salmonella typhimurium* (MRID # 43291721)	There was no evidence of a mutagenic response at any dose. Classification: Acceptable
Gene Mutation/*In vitro* assay in mammalian cells HPRT locus in Chinese Hamster Ovary (CHO) cells (MRID 44262814)	MB46513, (99.5% a.i.) did not induce forward mutations at the HPRT locus in CHO cells at any dose level tested. Classification: Acceptable
Cytogenetics/ *in vivo* mouse bone marrow micronucleus assay MRID 44263813)	**There was no significant increase in the frequency of MPCEs in bone marrow after any MB46513** (99.5%, a.i.) treatment time; therefore, the test article is considered negative in this micronucleus assay. Classification: Acceptable

I. Metabolism

Adequacy of data base for metabolism (Series 85-1, 85-2): The data base for metabolism (both 85-1 and 85-2) is considered to be complete. No additional studies are required at this time.

85-1 Metabolism - Rat

1. Studies Conducted with Fipronil

^{14}C-Fipronil (^{14}-C Fipronil, >97.0% radiochemical purity; unlabeled **Fipronil**, >99% a.i.) was administered orally in aqueous methylcellulose to groups (5 sex/dose) of male and female Sprague-Dawley rats at doses of 4 and 150 mg/kg (single dose) and 4 mg/kg x 14 days (repeated dose) (MRID # 42918655). The rate and extent of absorption

appeared similar among all dose groups, but may have been decreased at the high dose. Distribution data showed significant amounts of residual radioactivity in carcass, G.I. tract, liver, adrenals, and abdominal fat at 168 hours post-dose for all rats in all dose groups. Repeated low oral dosing or a single high oral dose resulted in an overall decrease in the amount of residual radioactivity found, but an increase in the amount in abdominal fat, carcass, and adrenals. Feces appeared to be the major route of excretion for **fipronil** derived radioactivity, where 45-75% of an administered dose was excreted. Excretion in urine was between 5-25%. Increases in the percentages excreted in urine and feces were observed with repeated low oral dosing or a single high dose, while the percentage found in all tissues combined decreased. There were no significant sex-related differences in excretion. Major metabolites in urine included two ring-opened products of the metabolite M&B 45,897, two oxidation products (M&B 46,136 and RPA200766), and parent chemical (M&B 46,030). In feces, parent M&B 46,030 was detected as a significant fraction of the sample radioactivity as well as the oxidation products M&B 46,136 and M&B 45,950. Whole blood half-life ranged from 149.4-200.2 hours in male and female rats at 4 mg/kg, with 0-168 hours AUCs approximately equal between sexes. At 150 mg/kg, whole blood half-life was noticeably decreased to 54.4 hours in male rats and 51.2 hours in female rats. Blood AUCs at this dose were approximately proportional to the increase in dose.

Classification: Minimum

2. Studies Conducted with Metabolite MB 46513

In a rat metabolism study (MRID 44262817), [U-^{14}C-phenyl] MB46513 (>99% a.i.) was administered to five Sprague-Dawley CD strain rats/sex/dose by gavage as a single dose at 1 or 10 mg/kg or as a single dose at 1 mg/kg following a 14-day pretreatment with unlabeled MB46513 at 1 mg/kg.

Within 168 hours of dosing, 93-101% of the administered dose was recovered from both sexes of each dose group, of which 46.4-69.5% was in the feces, 19.9-41.1% was in the tissues and carcass, and 4.4-10.8% was in the urine. In all test groups, fecal excretion was higher for males (60.1-69.5%) than for females (46.4-56.0%), and less radioactivity was retained in the carcasses and tissues of males (19.9-26.6%) than females (30.0-41.1%). Levels of urinary excretion were comparable between sexes. Excretion of the radioactivity was increased slightly by pretreatment and at the high dose level. Within 168 hours of dosing, the single low-dose (SOLD) animals excreted 51.6-67.1% of the dose in feces and urine (including cage wash), whereas the repeated low-dose (ROLD) animals excreted 66.4-73.7%, and the single high-dose (SOHD) animals excreted 69.9-80.6%. Radioactivity was excreted gradually by all dose groups, but the rate of excretion differed between dose groups. Fecal excretion peaked on Day-1 for the SOLD group, on Day-6 for the ROLD group, and on Day-5 for the SOHD group. Urinary excretion showed a similar pattern within dose groups. Maximum concentrations of radioactivity in blood were attained within 46 to 73 hours of dosing and were similar between sexes within dose group (low dose, 0.15 ppm; high dose, 2.03-2.31 ppm). For both dose groups, elimination half-lives were 156-170 hours for males and 210-221 hours for females. The ratio of the areas under the concentration curves (AUC) for high to low-dose animals was 15.2 for males and 10.9 for females, reflecting the difference in dose levels. The general distribution of radioactivity among tissues was the same between dose groups and sexes, although the actual levels differed between dose groups and sexes. Concentrations of radioactivity were highest in fat [fat/plasma ratios: 6.3-12.8 in males and 16.4-25.2 in females], followed usually by the adrenals and liver. Females also had high concentrations associated with the ovaries. The lowest concentrations of radioactivity were generally associated with the brain, spleen, muscle, whole blood, and stomach. With the exception of whole blood and plasma, concentrations of radioactivity in all tissues were generally higher for females than for males, e.g. radioactivity in fat was 1.6-2.8 times higher in females than in males. Among the dose groups, ^{14}C-residues were lowest in tissues from the SOLD group with the exceptions of residual carcass and skin plus fur. Pretreatment with MB46513 increased the residue levels in tissues, and residue levels in tissues from the SOHD group were 10-30 times higher than in tissues from the SOLD group. The major radioactive component identified in excreta was unchanged MB46513 (males, 28.6-44.2%; females, 35.4-39.6%), nearly all of which was found in the feces. Unchanged MB46513 in urine accounted for <0.1% of the dose. The only other components in excreta accounting for >5% of the dose were MB46400 (males, 5.7-10.6%; females, 3.1-7.1%) and the 4-cyano-5-(N)cysteine conjugate of MB46513 (males, 7.2-14.2%; females, 3.8-9.2%). Other minor components identified in excreta included: RPA 105048; the sulfate conjugate of MB46513 (≤2.4%); a 4-cyano-5-(N) cysteine glycine conjugate of MB46513 (0.7-3.8%); and a 5-(N) cysteine conjugate of MB46513 (1.9-3.5%). Within each dose group, the metabolite profile was the same among sexes, although metabolite levels were

generally higher in males than females. The metabolic profile was also similar between dose groups, although there were differences in the relative levels of metabolites. Pretreatment resulted in lower levels of MB46513 and higher levels of metabolites than in SOLD animals. Levels of MB46513 were similar in excreta of SOHD and SOLD groups, but levels of metabolites were generally higher for the SOHD group. These data indicate that fecal excretion of unchanged MB46513 is the principal pathway for elimination of MB46513 from rats. The metabolism of MB46513 in rats involves substitution of the trifluoromethyl or cyano groups on the pyrazole ring and/or sulfate, glucuronide, or glutathione conjugation at the amide on the pyrazole ring. The high levels of radioactivity in fat compared to blood and the prolonged elimination half-life indicate that there is a potential for bioaccumulation of MB46513 in fatty tissues.

This metabolism study in the rat is classified **Acceptable (Nonguideline)** as it is not a required guideline study. It is acceptable for the purposes for which it was intended (metabolism information on MB46513, a photolytic metabolite of **fipronil**) as a special study.

j. Dermal Absorption

85-2 Dermal Absorption - Rat

1. Studies Conducted with Fipronil

In this dermal absorption study (MRID: 43737308; Guideline No.: §85-2), male rats were dosed at 0.071, 0.688 and 3.88 mg/cm^2 for exposures of 0.5, 1, 2, 4, 10 and 24 hours with **fipronil**. Quantity of **fipronil** in washed skin was 1.14-2.45%, 0.60-3.29% and 0.35-0.80% at the respective doses. Quantity of **fipronil** absorbed was <1% at all doses. The system was saturated at 3.88 mg/cm^2. The dermal absorption rat was calculated to be <1% at 24 hours.

2. Studies Conducted with Metabolite MB 46513

In a dermal absorption study (MRID 44262816), 24 male Crl:CD BR rats/dose group were dosed dermally with [^{14}C]MB4613 (99% a.i.) as a 1% carboxymethylcellulose aqueous suspension at dose levels of 0.081, 0.881, or 7.17 mg/rat (0.006, 0.071, or 0.574 mg/cm^2). Four rats/dose were sacrificed for assessment of dermal absorption after 0.5, 1, 2, 4, 10, and 24 hours of exposure.

Dosed radioactivity was quantitatively recovered from each dose group (92.5-103%). After 24 hours of exposure, dermal absorption of MB46513 was minimal. For all dose groups, the majority of the dose was not absorbed (90.2-102.3%), and only trace amounts (≤0.1%) of radioactivity were excreted in the urine and feces. For the low- and mid-dose groups, radioactivity remaining in/on the skin after washing increased with the duration of exposure, reaching maximums of 3.97% and 1.05% of the dose, respectively, by 24 hours. However, duration of exposure had no effect on accumulation of radioactivity in/on the skin for the high-dose group. For the low-dose group, absorption (measured as amount excreted plus amount retained in the body) increased over time from <0.005% of the dose at 0.5 hours to 2.64% of the dose at 24 hours. Potential absorption (amount absorbed plus amount retained in/on skin) also increased over time from 0.74% of the dose at 0.5 hours to 6.61% of the dose at 24 hours. For the mid-dose group, absorption increased over time from <0.01% of the dose at 0.5 hours to 0.35% of the dose at 24 hours. Potential absorption increased from 0.28% of the dose at 0.5 hours to 1.40% of the dose at 24 hours. For the high-dose group, the maximum amount of absorption was 0.14% of the dose at 0.5 hours, and the maximum potential absorption was 0.66% of the dose at 4 hours.

SELECT DERMAL ABSORPTION VALUES
(Total % adhered to the skin and absorbed)

ave. dose	1 hour	10 hours	24 hours
0.006 mg/cm^2	<1	**2.35**	6.61
0.071 mg/cm^2	<1	<1	1.4
0.574 mg/cm^2	<1	<1	<1

There was 2.35% adhered to the skin and absorbed at the 10 hour time point with the lowest dose applied (0.006 mg/cm^2).

This study is classified as **Acceptable (Guideline)** and satisfies the requirement for a dermal absorption study **(§85-2)** in the rat.

k. Special Studies

1. Studies Conducted with Fipronil

1) Thyroid Function/Rat: Four groups of 27 male Crl:CD (SD) BR rats per group were administered either methylcellulose (vehicle control), 10 mg/kg/day fipronil (95.4% a.i.) l, 200 mg/kg/day propylthiouracil (PTU) or 50 mg/kg/day Noxyflex for 14 days. On Day 15, each animal received $Na^{125}I$ at a dose level of 1 µCi ^{125}I (MRID # 42977904). Six hours later, 9 males per group received either 10 or 25 mg/kg potassium perchlorate or 0.9% saline solution. The treatment with **fipronil** or Noxyflex appeared to result in stimulation of the thyroid glands as evidenced by increased accumulation of ^{125}I in the thyroid glands and by increases in the ratios of radioactive distribution between the blood and thyroid. These changes were accompanied by increases in thyroid weight. Treatment with PTU produced decreases in the amount of ^{125}I incorporated in the thyroid and in the blood:thyroid ratios along with elevated levels of ^{125}I in the blood. However, the weights of the thyroids from these animals were increased by over 2.5 fold compared to the controls and therefore, the ratio of ^{125}I in the blood to thyroid weight was reduced. The administration of perchlorate produced further reductions in the ^{125}I content in the thyroids and in the blood:thyroid ^{125}I radioactivity ratio. There was no evidence of an inhibition of iodide incorporation by either **fipronil** or Noxyflex.

Classification: Supplementary

2) Thyroxine Clearance: Six groups of six male Crl:CD (SD) rats per group were administered either **fipronil** (95.4%) (10 mg/kg/day by gavage), phenobarbital (80 mg/kg/day intraperitoneally) or 0.5% methylcellulose (vehicle control at 5 mL/kg by gavage) for a duration of either one day or fourteen days (MRID # 42918654. Four hours after the final dose of either test substance, each rat received [^{125}I] thyroxine at a dosage of 10 µCi/kg. **Fipronil** had no effect on mortality or other ante mortem parameters. Phenobarbital-treated animals were observed to have collapsed posture, lethargy and shallow breathing on the first day of treatment. There was no effect of **fipronil** on clearance after one day of treatment, however after 14 days, there was a decrease in terminal half life (52% of control level) and increases in clearance and volume of distribution (261% and 137% of control level, respectively). The effects seen with phenobarbital treatment were similar, although quantitatively not as severe and were evident on Day 1 of treatment.

Classification: Supplementary

3) 28-Day Study with **Fipronil**: Conclusions: Five Crl:CD (SD)BR rats/sex/group were treated with Fipronil (93% a.i.) l in the diet for four weeks at doses of either 0, 25, 50, 100, 200 or 400 ppm (3.4, 6.9, 12.6, 24.5 and 45.3 mg/kg/day, respectively for males; 3.5, 6.7, 12.9, 24.9 and 54.9 mg/kg/day, respectively, for females (MRID Number: 4402801)). One female in the 400 ppm group died during the treatment period; the cause of death could

not be determined. Group mean body weight was decreased in both sexes of the 200 and 400 ppm groups the first five days of the study, most likely due to decreased palatability. Overall (weeks 0-4) group mean body weight gain (BWG) was decreased by 18 and 23% in the 200 and 400 ppm group males, respectively. Overall BWG was decreased by 21, 24 and 26% in the 100, 200 and 400 ppm group females, respectively. Group mean food consumption was decreased for both sexes of the 100, 200 and 400 ppm groups at Day 5, but was comparable to the controls after one week for females and three weeks for males. There were no treatment-related changes in hematology parameters. Total protein and globulin were statistically increased in all the treated male and female groups; cholesterol was increased in the 400 ppm group males and all treated females. On gross pathological examination, the liver was enlarged in 5/5 male rats and 3/5 female rats in the 400 ppm group, 2/5 females in the 200 ppm group, 1/5 males in the 100 ppm group and 1/5 females in the 50 ppm group. Increased group mean liver weights were seen in all treated males and females, however the differences in males treated at 100 ppm and below were not statistically significant. Group mean thyroid weights were increased in all the treated females, however the differences were not statistically significant or dose-related. There was an increased incidence of follicular hypertrophy of the thyroids in all treated male and female rats. The change was graded as moderate in the male rats at 200 and 400 ppm and minimal in all other treated groups. A dose-related increase in generalized hepatocyte enlargement was seen in males and females in the 200 and 400 ppm groups and in males in the 100 ppm group.

The LOEL is ≤ 25 ppm (3.4 mg/kg/day in males; 3.5 mg/kg/day in females) based on clinical laboratory changes, increased absolute liver weights in females and histopathological alterations in the thyroid glands. The NOEL is < 25 ppm.

Classification: Acceptable (Nonguideline)

2. Studies Conducted with Photodegradate MB 46513

In a 28-day range-finding study (MRID 44262809), **MB 46513** (a metabolite of fipronil; 97.5% a.i.) was administered to Sprague-Dawley rats (10/sex/dose) in the diet at nominal dose levels of 0, 0.5, 3, 30 or 100 ppm (equivalent to 0, 0.04, 0.23, 2.20 or 3.74 mg/kg body weight/day, respectively, for males; 0, 0.04, 0.24, 2.32 or 3.8 mg/kg body weight/day, respectively, for females). In addition to evaluation of standard study parameters, thyroid hormone levels were measured on days 7 and 23.

No treatment-related effects were observed in the 3 and 0.5 ppm treatment groups. One male in the 30 ppm group was found dead on day 6 and all 100 ppm group animals died within the first 2 weeks of study. Clinical signs at 30 and 100 ppm included piloerection (M 9/10 and 4/10 at 30 and 100 ppm; F 5/10 and 6/10 at 30 and 100 ppm), curling up at handling (M 6/10 and 4/10 at 30 and 100 ppm; F 8/10 and 5/10 at 30 and 100 ppm); thin (M 5/10 and 4/10 at 30 and 100 ppm; F 6/10 and 6/10 at 30 and 100 ppm); increased motor activity (F 1/10 and 2/10 at 30 and 100 ppm) and irritability with convulsions at 100 ppm in 1 female. There was a decrease in body weight (9-18% and 26-36% for 30 and 100 ppm) and food consumption (8-34% and 69-73% for 30 and 100 ppm). Clinical chemistry parameters affected at 30 ppm included bilirubin (decrease - 28-33%) and aspartate aminotransferase (increased F - 22%). At 30 ppm on day 7 or 23, males had decreased T3 and T4 levels (33-49%) and females had decreased T4 levels (61%) compared to the controls. While at 100 ppm T3 levels were decreased 46% (females only), and T4 levels were decreased 50-63%. No treatment-related differences in hematology or urine parameters, organ weights or gross postmortem or microscopic appearance were observed.. No neoplastic tissue was observed. Ophthalmoscopic examinations were not conducted. **The LOEL for this study is 30 ppm (2.20 and 2.32 mg/kg/day for M and F, respectively), based on clinical signs including piloerection, curling up and thin appearance; and decreased body weights in both sexes. The NOEL is 3 ppm (0.23 and 0.24 mg/kg/day for M and F, respectively).**

This 28-day dietary feeding study is classified **acceptable (non-guideline)** as it is not a required guideline study. It is acceptable for the purposes for which it was intended. It is recommended that a maximum treatment rate between 3 and 30 ppm be used in longer term studies.

3. Studies Conducted with Metabolite MB 45897

In a subchronic toxicity study (MRID 44262821), MB 45897 (intermediate of fipronil; 99.7 a.i.) was administered to CD rats (5/sex/dose) by gavage at nominal dose levels of 0, 50, 200 or 1000 mg/kg/day for 4 weeks.

In the 1000 mg/kg/day treatment groups, the livers of males and females had increased absolute (32-58%) and relative (53-70%) weights, and the livers of 3/5 males exhibited periacinal hypertrophy with cytoplasmic vacuolation. Total plasma protein levels were increased (10-19%) in both sexes, and alanine aminotransferase activity (48%) was increased in females. All rats salivated excessively (days 2-28), and exhibited hunched posture (days 8, 9, 11, and 12), underactivity (days 8-13), and staggered gaits (day 8). Males (4-5) and females (2-3) had hair loss (days 3-28). Both sexes had reduced body weight gains (16%), and females were slightly anemic. In the 200 mg/kg/day treatment groups, all rats salivated excessively (days 3-28) and exhibited hunched posture (days 8 and/or 11 and 12). Males had increased (9%) total plasma protein levels. In the 50 mg/kg/day treatment groups, all rats salivated excessively (days 8-15, males; days 8-28, females) This may have been due to local irritation of the test material. No rats died as a result of treatment. Ophthalmoscopic exams and urinalysis were not conducted. No treatment-related differences in food consumption were observed in any treatment group. No neoplastic tissue was observed in treated or control rats. **The LOEL for this study is 200 mg/kg/day, based on hunched posture in all rats treated at this dose level. The NOEL is 50 mg/kg/day.**

This 4-week oral toxicity study is classified **acceptable (non-guideline)** as it is not a required guideline study. It is acceptable for the purposes for which it was intended, that being to assess the systemic toxic effects following 4 weeks of repeated daily administration (gavage) of the test substance.

4. Studies Conducted with metabolite RPA 200766

28-Day Study with RPA 200766: Conclusions: Ten Sprague-Dawley rats/sex/group were administered RPA 200766 (96.2% a.i.), a fipronil metabolite, in the diet at dose of either 0, 50, 500, 5000 or 15000 ppm for 28 days (mg/kg/day doses respectively: males - 3.80, 38.16, 385.07 and 1087.05; females - 4.44, 43.97, 386.75 and 1062.84)(MRID Number: 44017701). One female in the 15000 ppm group died during the study; the cause of death was attributed to difficulty in blood collection. Body weight was significantly decreased from Day 8 to Day 28 for males and females in the 5000 and 15000 ppm groups. Mean body weight gain over the course of the study was decreased by 27% and 61% in the 5000 and 15000 ppm group males, respectively; it was decreased by 46% and 77% for the 5000 and 15000 ppm group females, respectively. Mean food consumption over the course of the study was decreased by 11% and 25% in the 5000 and 15000 ppm group males, respectively; it was decreased by 22% and 33% in the 5000 and 15000 ppm group females, respectively. Mean hemoglobin values were decreased at 500 ppm and above for males and females; all were statistically significant, except for the 15000 ppm group females. Mean hematocrit values were decreased at 5000 ppm and above; all were statistically significant, except for the 15000 ppm group females. Mean corpuscular hemoglobin values were decreased in the 15000 group males and females and in the 5000 ppm group males. Mean cholesterol values were significantly increased in males and females at 500 ppm and above. Mean triglyceride values were increased in the 5000 and 15000 ppm group males and females. Urea nitrogen was increased in the 5000 and 15000 ppm group females, whereas creatinine values were increased in males at 500 ppm and above. There were no histopathological changes in the kidneys, therefore, these changes are of doubtful toxicological significance. Dose-related increases in absolute and relative liver weights were seen in males and females at 500 ppm and higher. Liver-to-brain weights were also increased in these groups. Significantly increased adrenal weights were seen in all the treated males. Thyroid weights were increased in males at 50 ppm and above, however the increases were not consistently found in all males in the group. In addition, there were no microscopic changes in the thyroid. Therefore, these findings are of questionable toxicological significance, although the parent compound, **fipronil**, is known to be a thyroid toxicant. Microscopic examination of the tissues from males and females in the 15000 ppm were not conducted. Slight to moderate hepatocellular hypertrophy was noted in the adrenals of males and females at 5000 ppm. Slight to moderate extra-medullary hematopoiesis was observed in males and females at 5000 ppm. A fine/coarse vacuolation of the zona fasciculata was observed in males at 50 ppm and higher and in females in the 5000 ppm group. **The NOEL was 50 ppm (3.80 mg/kg/day for males and 4.44 mg/kg/day for females). The LOEL was 500 ppm (38.16 mg/kg/day for males and 43.97 mg/kg/day for females) based on decreased hemoglobin values, increased cholesterol**

values and increased liver weights in both sexes.

Classification: Acceptable (Nonguideline)

l. Other Toxicological Considerations

i. Toxicity of the photodegradate MB46513 as compared to the parent fipronil

The **photodegradate MB46513** is not an animal metabolite. However in several toxicity studies it has been determined that it is more toxic that the parent **fipronil**. Since this **photodegradate** is present in rice it has been included in the dose response assessment below.

ii. Data gap for acute inhalation with the ICON™ 6.2FS formulation

This study (MRID 44260904) was classified by RD as **unacceptable** for the following reason;, 1) data too variable in both sexes, 2) it couldn't be determined whether the toxicity category was a I or II, 3) in addition the chamber concentration varied greater than 20 % in several doses, 4) and the particle size was only determined once per exposure in only 3 groups. This study needs to be repeated. Until this is done, the HED recommends that the formulation be considered a category I for inhalation exposure as it relates to labeling and protective clothing.

2. Dose Response Assessment

The HED Hazard Identification Assessment Review Committee met on July 10, 1997 to select appropriate endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) for **fipronil** and on 12/9/97 to select appropriate endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) for the fipronil **photodegradate.**

FIPRONIL

a. Special Sensitivity to Infants and Children

EPA generally defines the level of appreciable risk as exposure that is greater than 1/100 of the no observed effect level in the animal study appropriate to the particular risk assessment. This 100-fold uncertainty (safety) factor/margin of exposure (safety) is designed to account for inter-species extrapolation and intra-species variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and

post-natal toxicity and the completeness of the data base (resulting in a total factor of 1000) unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

On July 2, 1997, the Hazard Identification Committee evaluated the chemical fipronil for FQPA considerations. The following discussion represents the information that was considered and the following conclusions were drawn by the Committee.

i. Adequacy of data: An acceptable two-generation reproduction study in rats (MRID# 42918647) and acceptable prenatal developmental toxicity studies in rats (MRID#42977903) and rabbits (MRID# 42918646) have been submitted to the Agency, meeting basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. In addition, an acceptable developmental neurotoxicity study was conducted with fipronil and reviewed by the Agency. There are no data gaps for the assessment of the effects of fipronil on developing animals following *in utero* and/or early postnatal exposure.

ii. Susceptibility Issues: The data contained evidence of increased sensitivity of rats to alterations in functional development following pre- and/or postnatal exposure with fipronil. Specifically, in a developmental neurotoxicity study in rats, the developmental and developmental-neurotoxicity NOEL of 0.5 ppm (0.05 mg/kg/day) was lower than the maternal toxicity NOEL of 10 ppm (0.9 mg/kg/day). In the offspring, decreased pup weights, increased time of preputial separation in males, and increased motor activity counts in female pups were observed at the developmental LOEL of 10 ppm (0.9 mg/kg/day), while maternal toxicity (decreased body weight, body weight gain, and food consumption) was observed at the maternal LOEL of 200 ppm (15 mg/kg/day).

It was noted by the Committee that previously conducted studies with fipronil did not identify any issues of increased sensitivity in the fetuses or pups following pre- and/or postnatal exposure. In the prenatal developmental toxicity study in rats, there was no evidence of developmental toxicity at the highest doses tested (20 mg/kg/day). Maternal toxicity (decreased body weight gain, food consumption and/or water consumption) was observed at this dose (20 mg/kg/day) with the maternal NOEL established at 4 mg/kg/day. In the prenatal developmental toxicity study in rabbits, there was also no evidence of developmental toxicity at the highest doses tested (1.0 mg/kg/day).

Maternal toxicity (decreased body weight gain, food consumption and/or water consumption) was observed at this same dose (1.0 mg/kg/day) and lower, with the maternal NOEL established at <0.1 mg/kg/day.

Additionally, in the two-generation reproduction study in rats, offspring toxicity was observed only in the presence of parental toxicity. The offspring NOEL was 30 ppm (2.54-2.74 mg/kg/day), based upon clinical signs of toxicity, decreased litter size, decreased body weights, decreased pre- and postnatal survival, and delays in physical development at the LOEL of 300 ppm (26.0-28.4 mg/kg/day). In the parental animals, reproductive toxicity (reductions in mating and fertility) was also observed at the 30 ppm dietary level. The systemic NOEL for the parental animals was 3 ppm (0.25-0.27 mg/kg/day), based upon increased weight of the thyroid gland and liver in both sexes, decreased weight of the pituitary gland in the females, and increased incidence of thyroid follicular epithelial hypertrophy in the females at the LOEL of 30 ppm.

iii. Uncertainty Factor: The Committee noted that the developmental neurotoxicity NOEL of 0.05 mg/kg/day, when adjusted for 1% dermal absorption, yields an equivalent NOEL of 5 mg/kg/day, the value established as the systemic NOEL in the 21-day dermal study in rabbits. This value was selected for use in the short term and intermediate risk assessment calculations for fipronil. The NOEL used for the RfD calculation was 0.019 mg/kg/day from the combined chronic toxicity-carcinogenicity study in the rat, a value that is even lower than the NOEL used for short- and intermediate-term exposure. Therefore, it was concluded that the risk assessment calculations as defined, will provide adequate protection for sensitive subpopulations, including infants and children. **The Committee determined that the third Uncertainty Factor (UF) in the risk assessment of fipronil, under the provisions of the FQPA mandate to ensure the protection of infants and children, was not warranted for chronic or less than life time exposure and could be removed.**

HED believes that reliable data support using the 100-fold margin/factor, rather than the 1000-fold margin/factor, when EPA has a complete data base under existing guidelines, and when the severity of the effect in infants or children, the potency or unusual toxic properties of a compound, or the quality of the exposure data do not raise concerns regarding the adequacy of the 10-fold margin/factor.

iv. Recommendation for a Developmental Neurotoxicity Study: A neurotoxicity study is available and has been considered together with

the rest of the toxicity data base for fipronil.

b. Reference Dose (RfD)

The Hazard ID Assessment Review Committee (document dated September 4, 1997) assigned an **RfD of 0.0002 mg/kg/day** using a NOEL of 0.019 mg/kg/day and an uncertainty factor of 100; NOEL established from a combined chronic toxicity/ carcinogenicity study in rats; LOEL = 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day), based on an increased incidence of clinical signs (seizures and death) and alterations in clinical chemistry (protein) and thyroid parameters (increased TSH, decreased T4) at 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day).(MRID# 42918648).

c. Carcinogenic Classification and Risk Quantification

Cancer Classification and Basis: According to the proposed new guidelines, this chemical has been classified by the HED Cancer Peer Review Committee (document dated July 18,.1997) as a Group C - Possible Human Carcinogen, based on increases in thyroid follicular cell tumors in both sexes of the rat, which were statistically significant by both pair-wise and trend analyses. The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status. There was no apparent concern for mutagenicity (no mutagenic activity).

d. Developmental and Reproductive Toxicity

Fipronil is not classified as a developmental or reproductive toxicant.

e. Dermal Absorption

% Absorbed: < 1% at 24 hours based on a dermal absorption study (MRID# 42918635).

f. Other Toxicological Endpoints

i. Acute Dietary (one day)

Dose and endpoint for use in risk assessment: **NOEL - 0.5 mg/kg** in an acute neurotoxicity study in rats, based on decreased hind leg splay in male and female rats observed at LOEL = 5 mg/kg (MRID# 42918635).

This risk assessment is required.

ii. Short- and Intermediate-Term Occupation and Residential (dermal and inhalation)

Dose and endpoint for use in risk assessment: Critical study: 21-day dermal **NOEL = 5 mg/kg/day** based on decreased body weight gain and food consumption in male and female rabbits observed at the LOEL of 10 mg/kg/day (MRID# 42918644). Supporting study: Developmental toxicity and developmental neurotoxicity **NOEL = 0.5 ppm** (0.05 mg/kg/day). Developmental LOEL was 10 ppm (0.9 mg/kg/day) based on decreased mean pup weights during lactation and a significant increase in time to preputial separation in male rats. The developmental neurotoxicity LOEL was 10 ppm (0.9 mg/kg/day) based on an increase in mean motor activity counts for females on Postnatal Day 17 (MRID# 44039002).

Comments about study and/or endpoint: The NOEL established after dermal administration in the 21-day dermal toxicity study is 5 mg/kg/day. When the co-critical study NOEL based on oral administration in the developmental neurotoxicity study, 0.05 mg/kg/day is corrected for the less than 1% dermal absorption, exposure is essentially the same as the critical study (5 mg/kg/day).

This risk assessment is required.

iii. Chronic Occupation and Residential (Non-Cancer)

Dose and endpoint for use in risk assessment: In a combined chronic toxicity/carcinogenicity study [rat], the **NOEL is 0.5 ppm** (M: 0.019 mg/kg/day; F: 0.025 mg/kg/day), based on an increased incidence of clinical signs (seizures and death) and alterations in clinical chemistry (protein) and thyroid parameters (increased TSH, decreased T4) at 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day) (MRID# 42918648).

Comments about study and/or endpoint: Since the NOEL identified is from an oral study, a dermal absorption factor of < 1% should be used in risk calculations. NOTE: This study/dose was also used to establish the RfD.

This risk assessment is required.

iv. Inhalation Exposure (Any time period)

There are three critical acute inhalation studies, one with the technical and two with formulations.

Critical Study 1: Acute inhalation study (technical) - Guideline §81-3, MRID No. 43544401

Executive Summary: Sprague-Dawley rats (5/sex) were exposed nose-only to fipronil at doses of 0.33, 0.52 and 0.72 mg/L for four hours. At 0.72 and 0.52 mg/L, 100% mortality was observed. At the 0.33 mg/l exposure, 2 male rats died, one on day 1 post-exposure and 1 on day 6 post-exposure. At the 0.72 mg/l dose, the following were noted in all rats on the day of exposure: urogenital, body and periocular wetness; unkempt fur; fine whole body tremors. In one male at this dose, incoordination was observed on post-exposure days 4 through 7, hyperactivity on post-exposure day 4 and hypoactivity and swollen penis on post-exposure day 7. This rat died on day 8. In one female rat at this dose, perioral, perinasal and periocular red encrustation was observed on post-exposure days 1 through 11, hyperactivity on post-exposure days 2 through 4, hypoactivity on post-exposure days 7 through 10 and incoordination on post-exposure days 6 through 11. This rat died on day 12. At the 0.52 mg/L dose, the same signs as mentioned for all rats at the 0.72 mg/L exposure concentration were observed without any additional signs. At the 0.33 mg/L dose, similar signs were recorded, with the following additions in males: perioral, perinasal, and periocular red encrustation up to day 5 post-exposure; incoordination in 4 of 5 male rats up to post-exposure day 3; hypoactivity in 4 of 5 male rats up to post-exposure day 2. In female rats at this exposure concentration, similar signs were observed as for males. The incoordination did not appear until post-exposure day 3 in 4 of 5 female rats and did not last beyond this point. The LC_{50} in rats was 0.36 mg/L, 0.42 mg/L and 0.39 mg/L in males, females and the combined sexes, respectively (Toxicity Category II).

Critical Study 2: Acute inhalation study (1.6% formulation) - Guideline §81-3, MRID No. 42918638

$LC_{50} > 5.11$ mg/L (Toxicity Category IV)

Critical Study 3: Acute inhalation study (0.242% formulation) - Guideline §81-3, MRID No. 43121106

$LC_{50} > 5.06$ mg/L (Toxicity Category IV)

Dose and Endpoint For Use in Risk Assessment: None

Comments and Rationale: In the acute inhalation study, death occurred at the lowest dose tested. At the next higher dose, there were deaths and clinical signs of toxicity. The lack of a NOEL in an

inhalation study with the technical chemical would usually require an additional Uncertainty Factor. However, using the lowest dose in the acute inhalation study (0.33 mg/L) and available exposure data demonstrated an adequate margin of exposure (>68,000).

Therefore a separate risk assessment is not required.

MB46513

a. Special Sensitivity to Infants and Children

On December 9, 1997, the Hazard Identification Assessment Review Committee evaluated the chemical **MB46513 a photodegradate** of fipronil for FQPA considerations. The following discussion represents the information that was considered and the following conclusions were drawn by the Committee.

I. Adequacy of data: There are no data gaps for the assessment of the effects of **Fipronil** and/or the **photodegradate** on developing animals following *in utero* and/or early postnatal exposure.

ii. Susceptibility Issues: In determining sensitivity, the toxicity of the **photodegradate MB46513** and the parent compound will be considered simultaneously. The oral perinatal and prenatal data with the parent compound **Fipronil** demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* exposures. No additional sensitivity was identified in the prenatal developmental toxicity study in rats following *in utero* exposure to Fipronil **photodegradate MB46513**.

(a) Developmental Toxicity

In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/group) received oral administration of **Fipronil photodegradate MB 46513** (99.2%) in aqueous methylcellulose (10 mL/kg) at dose levels of 0, 0.5, 1.0, or 2.5 mg/kg/day during gestation days 6 through 15. The dams were sacrificed on gestation day 20. For maternal toxicity, the NOEL was 1.0 mg/kg/day and the LOEL was 2.5 mg/kg/day based on an increase in clinical signs of toxicity (hair loss) and on reduced body weight gain, food consumption, and food efficiency. For developmental toxicity, the NOEL was 1.0 mg/kg/day and the LOEL was 2.5 mg/kg/day based on a slight increase in fetal and litter incidence of reduced ossification of several bones (hyoid,

5th/6th sternebrae, 1st thoracic vertebral body, pubic bone, and 1 or 2 metatarsi). [Note that most of the reduced ossification is weak evidence of a developmental effect. Although the minor decrement in fetal weight at 2.5 mg/kg/day has questionable biological relevance, the decrement is supported by the delayed ossification.] (MRID No. 44275001).

In both the prenatal developmental toxicity studies in rats and rabbits with **Fipronil,** there was no evidence of developmental toxicity at the highest doses tested (20 mg/kg/day in rats and 1.0 mg/kg/day in rabbits). Maternal toxicity (decreased body weight gain, food consumption and/or water consumption) was observed at these same doses, with a maternal NOEL of 4 mg/kg/day for rats and <0.1 mg/kg/day for rabbits (MRID Nos. 42977903 and 42918646) .

(b) Reproduction Toxicity

In the two-generation reproduction study in rats with **Fipronil,** offspring toxicity was observed only in the presence of parental toxicity. In the parental animals, reproductive toxicity (reductions in mating and fertility) was also observed at the 30 ppm dietary level. For parental systemic toxicity, the NOEL was 3 ppm (0.25-0.27 mg/kg/day) and the LOEL was 30 ppm (2.54-2.74 mg/kg/day) based on increased weight of the thyroid gland and liver in both sexes, decreased weight of the pituitary gland in the females, and increased incidence of follicular epithelial hypertrophy in the females. For offspring toxicity, the NOEL was 30 ppm (2.54-2.74 mg/kg/day) and the LOEL was 300 ppm (26.0-28.4 mg/kg/day) based upon clinical signs of toxicity, decreased litter size, decreased body weights, decreased pre- and postnatal survival, and delays in physical development. (MRID No.42918647) .

(c) Developmental Neurotoxicity

In a developmental neurotoxicity study in rats with **Fipronil,** there was evidence of increased sensitivity of offspring to alterations in functional development following pre- and/or postnatal exposure. Specifically, the developmental and developmental-neurotoxicity, the NOEL of 0.5 ppm (0.05 mg/kg/day) was lower than the maternal toxicity NOEL of 10 ppm (0.9 mg/kg/day). In the offspring, decreased pup weights, increased time of preputial separation in males, and increased motor activity count in female pups was observed at the

developmental LOEL of 10 ppm (0.9 mg/kg/day), while maternal toxicity (decreased body weight, body weight gain, and food consumption) were observed at the developmental LOEL of 200 ppm (15 mg/kg/day) (MRID No. 44039002).

iii. Uncertainty Factor: The Committee determined that for the Fipronil **photodegradate MB 46513**, the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** This conclusion was based on the following factors.

(a) Developmental toxicity studies in rats with **Fipronil** as well as the **photodegradate MB46513** showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures.

(b) Developmental toxicity study in rabbits with **Fipronil** showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures.

© A two generation reproduction toxicity study in rats with **Fipronil** showed no increased sensitivity in pups when compared to adults.

(d) Sensitivity was defined in the developmental neurotoxicity study in rats with **Fipronil.** The NOEL is well defined for the offspring for the **photodegradate MB46513** as well as **Fipronil,** the parent compound.

(e) The toxicology profiles of the parent and the **photodegradate** indicates that there is a 10 fold difference in toxicity potency for the photodegradate when compared to the **parent** compound. Therefore, a 10 fold potency factor was used in the dose used to derive the RfD.

iv. Recommendation for a Developmental Neurotoxicity Study: A developmental neurotoxicity study was not recommended for **MB46513** (a fipronil photodegradate). A developmental neurotoxicity study was however conducted for the parent, **fipronil**.

b. Reference Dose (RfD)

The Hazard ID Assessment Review Committee (document dated December 18, 1997) assigned an RfD of 0.00002 mg/kg/day (Study MRID 42918648),

based on an adjusted NOEL of 0.019 mg/kg/day for the photodegradate (see discussion below relating to the adjusted NOEL) and an Uncertainty Factor of 100. Effects seen at the LOEL, 0.059 mg/kg/day were an increased incidence of clinical signs indicative of neurotoxicity as well as alterations in clinical chemistry and thyroid parameters.

Dose and Endpoint for establishing the RfD: Adjusted NOEL = 0.0019 mg/kg/day for the **photodegradate MB46513.** This adjusted dose was derived by the application of a Potency Adjustment Factor (PAF) of 10 to the chronic NOEL of 0.019 mg/kg/day for the parent compound (i.e., NOEL of 0.019 mg/kg/day ÷10 PAF = 0.0019 mg/kg/day) (see section **III.B.2. MB46513 a.iii.(e).)**

Comments about Study, Dose and Endpoint: The toxicity profile of the Fipronil **photodegradate MB46513** indicate this material to be *approximately* 10 times more potent than the parent compound when the NOELs/LOELs are compared. A comparison of the NOELs/LOELs established for the **Photodegradate and Fipronil** are presented below:

STUDY	**Photodegradate**	**Fipronil**
Acute Oral	LD_{50}= 16 mg/kg	LDLD5092 mg/kg
28-Day Oral - Rat	NOEL/LOEL = 0.23 / 2.2 mg/kg/day	NOEL/LOEL = 3.4 mg/kg/day (LDT)
90-Day Oral - Mouse	NOEL/LOEL = 0.08 / 0.32 mg/kg/day	NOEL/LOEL = 1.7 / 3.2 mg/kg/day
90-Day Oral - Rat	NOEL/LOEL = 0.029 / 0.18 mg/kg/day	NOEL =0.33 / 1.9 mg/kg/day
Developmental -Rat	Maternal NOEL/LOEL = 1 / 2.5 mg/kg/day Develop. NOEL/LOEL = 1 / 2.5 mg/kg/day	Maternal NOEL/LOEL = 4 / 20 mg/kg/day Develop. NOEL/LOEL= 20 mg/kg/day (HDT)

As shown above, results of acute oral as well as the 28 day and 90 day subchronic oral studies and oral developmental studies consistently demonstrated an approximately 10-fold greater potency of the **photodegradate MB46513** as compared to the parent compound, **Fipronil.**

For **Fipronil,** the RfD was derived from the NOEL of 0.019 mg/kg/day established in a combined chronic toxicity/carcinogenicity study in rats and an Uncertainty Factor (UF) of 100 for inter-and intra-species variation. The LOEL of 0.059 mg/kg/day was based on thyroid hypertrophy and neurological signs.

Since no long-term (chronic or carcinogenicity) studies are available for the **photodegradate**, the Committee concluded that there is sufficient experimental evidence to warrant the application of a 10 fold Potency Adjustment Factor

(PAF) to the chronic NOEL for the parent compound to calculate a chronic NOEL for the degradate in the absence of test data on the chemical. Thus, the application of the adjustment factor to the chronic rat NOEL of 0.019 mg/kg/day for the parent resulted in a adjusted chronic NOEL of 0.0019 mg/kg/day for the degradate.

Uncertainty Factor (UF): An UF of 100 was applied to account for inter (10 x)- and intra-(10 x) species variation.

$$RfD = \frac{(Adjusted\ NOEL = 0.0019 mg/kg/day)}{100(UF)} = (0.00002\ mg/kg/day\ rounded\ off)$$

Chronic Dietary Risk Assessment: The Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** For chronic dietary risk assessment, **a UF of 100 is adequate** for the protection of the general U.S. population including infants and children from exposure to the **photodegradate MB46513.** A UF of 100 following a 10-fold adjustment of the NOEL for **Fipronil** to account for the increase in potency of the **photodegradate** is adequate. See section **III.2. MB46513 a.iii.(a) through (e)** for the factors used in the weight-of-the-evidence considerations.

c. Carcinogenic Classification and Risk Quantification

No carcinogenicity studies are available with the **photodegradate MB46513**. **Fipronil**, the parent compound, was classified as a **Group C Carcinogen** (Possible Human Carcinogen) by the HED's Carcinogenicity Peer Review Committee (CPRC). The CPRC based this classification on statistically significantly (pair-wise and trend analyses) increased incidences of thyroid follicular cell tumors in both sexes of Charles River CD rats. The CPRC recommended that the RfD methodology for the quantification of human risk be used because the thyroid tumors appeared to be related to a disruption in the thyroid-pituitary status and there was no apparent concern for mutagenicity or available information from structurally related analogs (Memorandum: V. Dobozy, HED to R. Keigwin, RD, dated July 18,1997).

d. Developmental and Reproductive Classification

The **photodegradate, MB46513** is not classified as a developmental or reproductive toxicant.

e. Dermal Absorption

% Absorbed: Approximately 2% at 10 hours based on a dermal absorption study (MRID# 44262816).

f. Other Toxicological Endpoints

I. Acute Dietary

Dose and Endpoint for Risk Assessment: **NOEL=2 mg/kg** in an acute neurotoxicity study in rats (with the photodegradate) based on significant decreases in locomotor activity in both sexes during the first 30 minutes as well as decreases in hindlimb splay and rectal temperature in both sexes at 6 hours post dosing at 12 mg/kg/day (LOEL). (44262808)

Comments about Study and Endpoint: Effects were seen on the day of treatment after a single oral exposure (dose) and thus is appropriate for this risk assessment.

This risk assessment is required.

Although a developmental neurotoxicity study with the parent compound **Fipronil** was available (MRID No. 4403902), the Committee did not use this study for acute dietary risk assessment. In that study, the developmental and developmental neurotoxicity NOEL was 0.05 mg/kg/day and the LOEL was 0.9 mg/kg/day. The developmental LOEL was based on significant decreases in group mean pup weight during lactation and significant increase in time of preputial separation in males and the developmental neurotoxicity LOEL was based on a significant increase in mean locomotor activity counts in females on Postnatal Day 17. The Committee determined that these effects are not attributable to a single exposure (dose) and therefore are not appropriate for acute dietary risk assessments.

Acute Dietary Risk Assessment: The Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** For acute dietary risk assessment, **a Margin of Exposure (MOE) of 100 is adequate** for the protection of the general U.S. population including infants and children from acute exposure to Fipronil **photodegradate MB 46513.** A MOE of 100 is adequate. See section **III.2. MB46513 a.iii.(a) through (e)** for the factors used in the weight-of-the-evidence considerations.

ii. Short- and Intermediate Term Dermal Exposure (1 to 7 days) (1 week to several months)

Dose and Endpoint for Risk Assessment: Adjusted Dose= 0.5 mg/kg/day. This dose was derived by dividing the actual study NOEL

of 5 mg/kg/day by the Potency Adjustment Factor (PAF) of 10 (5÷10 = 0.5 mg/kg/day). The LOEL was based on decreases in body weight gain and food consumption. (42918644)

Comments about Study and Endpoint: The Committee selected the dose and endpoint from the 21-day dermal study with the **parent compound** for the following reasons: 1) a 21-dermal toxicity study with the **photodegradate** is not available; 2) low potential for risk from dermal exposure due to minimal dermal absorption as indicated for both the parent (<1%) and the **photodegradate** (2%) materials; and 3) when the developmental/developmental neurotoxicity NOEL of 0.05 mg/kg/day for **Fipronil** (established in the developmental neurotoxicity study) is adjusted for 1% dermal absorption (DA), results in a comparable dermal dose of 5 mg/kg/day (i.e., 0.05 mg/kg/day ÷ 1% DA = 5 mg/kg/day) which essentially is the same as the NOEL for **Fipronil** in the 21-day dermal toxicity study.

A MOE of 100 is adequate for short and intermediate occupational and/or residential exposures to Fipronil **photodegradate MB 46513.** A MOE of 100 is adequate for the same reasons stated under Acute and Chronic dietary exposure risk assessments. MOE's for Long-Term dermal and inhalation (anytime period) exposures are not required since use pattern does not indicate a potential for exposures via these routes.

This risk assessment is required.

iii. Chronic Dermal Exposure (Several Months to Lifetime)

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: Based on the current use pattern for the **photodegradate** (i.e., 1 application/year), Long-Term exposure via the dermal route is not expected.

This risk assessment is **NOT** required.

iv. Inhalation Exposure (Any time period)

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: The use pattern (i.e., 1 application/year) and the method of application does not indicate a potential for exposure via the inhalation route.

This risk assessment is **NOT** required.

v. Recommendation for Aggregate Exposure Risk Assessments

An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate due to differences in the toxicity endpoints observed between the oral (neurotoxicity and alterations in clinical chemistry and thyroid parameters) and dermal (decreases in body weight gain and food consumption) routes. An aggregate oral and inhalation risk is not required due to the lack of exposure potential via the inhalation route based on the current use pattern.

TABLE 2 ENDPOINTS FOR FIPRONIL (Parent)

EXPOSURE DURATION	EXPOSURE ROUTE	ENDPOINT AND TOXICOLOGICAL EFFECT
Acute	Dietary	NOEL: 0.5 mg/kg based on decreased hind leg splay in male and female rats in an acute neurotoxicity study in rats. MOE = 100 (includes FQPA considerations)
Short-Term (1-7 days) Occupational/Residential	Dermal	NOEL: 5 mg/kg/day based on ↑ body weight gain and food consumption in ♂s and ♀s in a 21-day dermal study in rabbits. Supported by a NOEL of 0.05 mg/kg/day in a developmental neurotoxicity rat study based in ↓ pup weight during lactation, an ↑ in time to preputial separation in males, and an ↑ in mean motor activity counts for ♀ on Postnatal Day 17. MOE = 100 (includes FQPA considerations)
Intermediate-Term (1 week - several months) Occupational/Residential	Dermal	Same as Short Term MOE = 100 (includes FQPA considerations)
Chronic-Term (several months-lifetime) Occupational/Residential	Dermal	NOEL: 0.019 mg/kg/day based on ↑ incidence of seizures and death, and alterations in clinical chemistry (protein) and ↑ TSH, ↓ T4. MOE = 100 (includes FQPA considerations)
All time periods	Inhalation	Not required
Cancer	Dietary/Dermal/ Inhalation	**Group C - Possible Human Carcinogen** (increases in thyroid follicular cell tumors with fipronil (M&F)). Use RfD to estimate human risk.
Chronic (non-cancer)	Dietary	RfD: 0.0002 mg/kg/day NOEL: 0.019 mg/kg/day based on ↑ incidence of seizures and death, alterations in clinical chemistry (protein) and ↑ TSH, ↓ T4. UF = 100 (includes FQPA considerations)

TABLE 3. ENDPOINTS FOR PHOTODEGRADATE (MB46513)

EXPOSURE DURATION	EXPOSURE ROUTE	ENDPOINT AND TOXICOLOGICAL EFFECT
Acute	Dietary	NOEL: 2.0 mg/kg based on decreases in locomotor activity as well as decreases in hindlimb splay and rectal temperature in an acute neurotoxicity study. MOE = 100 (includes FQPA considerations)
Short-Term (1-7 days) Occupational/Residential	Dermal	*Adjusted NOEL: 0.5 mg/kg/day based on decreases in body weight gain and food consumption in a 21-day dermal study. MOE = 100 (includes FQPA considerations)
Intermediate-Term (1 week - several months) Occupational/Residential	Dermal	*Adjusted NOEL: 0.5 mg/kg/day based on decreases in body weight gain and food consumption in a 21-day dermal study. MOE = 100 (includes FQPA considerations)
Chronic-Term (several months-lifetime) Occupational/Residential	Dermal	Not Applicable Use pattern (1 application/year) does not indicate a potential for this exposure; risk assessment not required. MOE = Not Applicable
All time periods	Inhalation	Not Applicable Use pattern (1 application/year) does not indicate a potential for this exposure; risk assessment not required. MOE = Not Applicable
Cancer	Dietary/Dermal/ Inhalation	**Group C - Possible Human Carcinogen** (increases in thyroid follicular cell tumors with fipronil (M&F)). Use RfD to estimate human risk.
Chronic (non-cancer)	Dietary	RfD: 0.00002 mg/kg/day * Adjusted NOEL: 0.0019 mg/kg/day based on neurotoxic clinical signs and alterations in clinical chemistry and thyroid parameter seen in a combined/ chronic toxicity study in the rat. UF = 100 (includes FQPA considerations)

* = Adjusted NOEL obtained by dividing the actual NOELs established in the studies conducted with the parent compound **Fipronil** and Potency Adjustment Factor of 10. A Potency Adjustment Factor of 10 was determined by the Committee based on the toxicity profiles of the **photodegradate MB41513** and **Fipronil.**

Chronic Dietary	Adjusted NOEL=0.0019 *	Neurotoxic clinical signs and alterations in clinical chemistry and thyroid parameter	Combined/ Chronic Toxicity - Rat	UF= 100
Short-Term (Dermal)				100
Intermediate-Term (Dermal)	Adjusted NOEL=0.5 *	Decreases in body weight gain and food consumption	21-Day Dermal	100
Long-Term (Dermal)		Not Applicable Use pattern (1 application/year) does not indicate a potential for this exposure; risk assessment not required.		
Inhalation	Not Applicable	Use pattern/method does not indicate a potential for exposure via this route; risk assessment not required.		

3. Dietary Exposure and Risk Assessment/Characterization

a. Dietary Exposure (Food Source)

I. Directions for Use

The petitioner provided specimen labels for an 80% water-dispersible granular (WDG) formulation (Product name = ICON™ 80 WG Insecticide), a 56% flowable solid (FS) formulation (Product name = ICON™ 6.2 FS Insecticide) and a 56% soluble concentrate (SC) formulation (Product name = ICON™ 6.2 SC Insecticide) proposed for use on rice for the control of rice water weevil. The proposed use patterns for rice are described below.

These formulations are proposed for a single preplant broadcast application to the soil of dry-seeded rice and water-seeded rice at 0.025-0.05 lb ai/A. For dry-seeded rice, fipronil is to be applied as a broadcast treatment to a dry soil surface prior to planting. For water-seeded rice, fipronil is to be applied as a broadcast treatment to a dry soil surface and incorporated prior to establishing a flood for water seeding. The labels specify that to prevent loss of insecticidal activity, fipronil must be incorporated within 48 hours of application. Fipronil is to be mixed with water and incorporated into the top 2-3 inches of soil. The labels state that application may be made using either aerial or ground equipment. For application using ground equipment, fipronil is to be sprayed in 10-40 gal/A; for aerial equipment, a minimum of 5 gal/A.

The labels propose a plantback interval of 5 months for root crops and

leafy vegetables, and a rotational crop restriction of 12 months for small grains or other rotational crops. A restricted entry interval of 12 hours is specified. The labels prohibit the feeding of rice straw to livestock, the grazing livestock on treated fields, and the fishing or commercial growing of fish, shellfish, or crustaceans on treated rice acreage. The labels specify that applications are not to be made directly to water, to areas where surface water is present, to intertidal areas below the mean high water mark, or on blooming crops or weeds.

The 6.2 FS formulation is also proposed for use as a seed treatment at a rate of 0.025-0.05 lb ai/A. For water-seeded rice, fipronil is to be applied after germination. Use of an EPA-registered dye is required.

ii. Nature of the Residue - Plants

Rhône-Poulenc has submitted data from a study (MRID 43827002) investigating the metabolism of uniformly phenyl-ring labeled [^{14}C]fipronil in rice. The qualitative nature of the residue in rice is adequately understood based on this metabolism study in which rice plants were separately treated with [phenyl-^{14}C]fipronil as a granular application and a foliar application. The total radioactive residues (TRR) were 0.755 ppm in/on immature rice plants (stem and leaves), 0.801 ppm in the solvent wash of immature plants, and 0.120 ppm in/on immature roots harvested 1 day following the last of two foliar spray applications of [^{14}C]fipronil at a total rate 0.054 lb ai/A/season (1.2x the maximum proposed seasonal rate). The TRR were 0.101 ppm in/on mature rice roots, 0.247 ppm in/on mature rice straw, 2.096 ppm in/on panicle, 0.495 ppm in/on husk, 0.155 ppm in/on bran, 0.024 ppm in/on brown rice, and 0.013 in/on polished rice harvested 42 days following treatment.

Approximately 47->100% of TRR were characterized/identified in rice commodities receiving foliar treatment. Fipronil was detected in all rice commodities, at 35.9-80.0% of TRR (0.096-0.271 ppm) in immature commodities and 22.7-51.6% of TRR (0.005-0.478 ppm) in mature commodities. The photodegradate MB 46513 was also detected in all commodities, at 7.1-13.2% of TRR (0.016-0.053 ppm) in immature commodities and 1.5-26.9% of TRR (<0.001-0.565 ppm) in mature commodities. The metabolites MB 45950, MB 46136, MB 45897, RPA 200766, and RPA 104615 were also identified.

The TRR were 0.053 ppm in/on immature rice plants (stem and leaves), 0.001-0.005 ppm in immature plant solvent washings, and 0.070 ppm in/on immature rice root harvested 31 days following a

single granular broadcast application of [^{14}C]fipronil at 0.045 lb ai/A (1x the maximum proposed seasonal rate). The total radioactive residues were 0.066 ppm in/on mature rice roots, 0.099 ppm in/on mature rice straw, 0.326 ppm in/on panicle, 0.073 ppm in/on husk, 0.022 ppm in/on bran, 0.005 ppm in/on brown rice, and 0.004 in/on polished rice harvested 72 days following treatment.

Approximately 48->100% of TRR were identified in rice commodities receiving granular treatment. Fipronil was detected in all rice commodities, at 14.8-15.3% of TRR (0.008-0.010 ppm) in immature commodities and 6.3-25.4% of TRR (0.001-0.027 ppm) in mature commodities. The photodegradate MB 46513 was also detected in all commodities, at 11.7-17.9% of TRR (0.008-0.010 ppm) in immature commodities and <1-74.3% of TRR (<0.001-0.242 ppm) in mature commodities. The metabolites MB 45950, MB 46136, MB 45897, RPA 200766, and RPA 104615 were also identified.

Because no evidence of ring cleavage was observed in an aerobic soil metabolism study, The Branch has previously waived the requirements for metabolism studies and confined rotational crop studies utilizing a test substance labeled in the pyrazole ring (CBTS No. 15943, D217612, 8/29/95, G. Kramer). The Branch will extend this decision to rice, and concludes that a rice metabolism study using pyrazole-labeled fipronil is not required.

The HED Metabolism Committee, in a meeting held on 5/28/97, has determined that the fipronil residues of concern for the tolerance expression and dietary risk assessment in plants and animals are the parent and its metabolites MB 46136 and MB 45950. The Committee also concluded that residue data for metabolite MB 46513 will be required for crops for which metabolism data indicate that this metabolite comprises a significant portion of the total radioactive residue (i.e., rice, potatoes, and rotational crops).

Metabolite MB 46513 was identified as a significant component in/on rice commodities. The Agency, therefore, concurs with the petitioner that the residues of concern for the proposed tolerances are fipronil and its metabolites MB 45950, MB 46136, and MB 46513.

iii. Nature of the Residue - Animals

Ruminants

Rhône-Poulenc has submitted a ruminant metabolism study (MRID 44262837) investigating the metabolism of [^{14}C]MB 46513 in

lactating goats. MB 46513 is a photodegradate of fipronil which was identified in rice and cotton metabolism studies and in the confined rotational crop study but was not identified in previously submitted/evaluated ruminant or poultry metabolism studies. The test substance, phenyl-labeled [^{14}C]MB 46513 was administered orally to each of three lactating goats twice daily for 7 consecutive days at respective does rates of 10 ppm, 2 ppm, and 0.05 ppm. An additional goat served as a control. The submitted ruminant metabolism study for MB 46513 is acceptable. Following oral administration of [^{14}C]MB 46513 to lactating goats at 10 ppm in the diet for 7 days, the TRR were 0.0502-0.3580 ppm in milk, 2.815 ppm in liver, 0.468 ppm in kidney, 0.180 ppm in muscle, and 2.681 and 2.215 ppm in omental and renal fat, respectively. MB 46513 was the major component identified at 93.8% of TRR (0.164 ppm) in 32-h milk, 94.1% of TRR (0.337 ppm) in 152-h milk, 58.1% of TRR (1.637 ppm) in liver, 49.2% of TRR (0.230 ppm) in kidney, 69.6% of TRR (0.125 ppm) in muscle, 81.6% of TRR (2.188 ppm) in omental fat, and 85.6% of TRR (1.896 ppm) in renal fat. Three additional metabolites were tentatively identified in liver: 5-deaminated ring-opened RPA 105048 (3.42% of TRR, 0.096 ppm), RPA 108058 (2.06% of TRR, 0.058 ppm), and 5-deaminated ring-opened RPA 106889 (2.96% of TRR, 0.083 ppm).

Poultry

Rhône-Poulenc has submitted data from a study (MRID 44262836) investigating the metabolism of MB 46513 in laying hens. MB46513 is a photodegradate of fipronil which was identified in rice and cotton metabolism studies and in the confined rotational crop study but was not identified in ruminant or poultry metabolism studies. The test substance, phenyl-labeled [14C]MB46513 was administered orally to each of three groups of five laying hens once daily for 14 consecutive days at respective dose rates of 10 ppm, 2 ppm, and 0.05 ppm. Three hens served as controls. The submitted poultry metabolism study for MB 46513 is acceptable. Following oral administration of [^{14}C]MB 46513 to laying hens at 10 ppm in the diet for 14 days, the TRR were 0.843 ppm in egg whites, 7.182 ppm in egg yolks, 4.089 ppm in liver, 0.508 ppm in muscle (breast and thigh), 9.683 ppm in omental fat, and 5.891 ppm in skin with fat.

MB 46513 was the major component identified at 83.3% and 85.1% of TRR (0.350 ppm and 0.717 ppm) in Day 5 and Day 14 egg whites, 56.37% and 59.33% of TRR (0.827 ppm and 4.261 ppm) in Day 5 and Day 14 egg yolks, 13.83% of TRR (0.565 ppm) in liver, 69.68% of TRR (0.354 ppm) in muscle, 90.9% of TRR (8.802 ppm) in omental fat, and 86.9% of TRR (5.119 ppm) in skin with fat. In addition, RPA

108058 was tentatively identified in Day 5 egg yolks (2.53% of TRR, 0.037 ppm), and Day 14 egg yolks (1.23% of TRR, 0.088 ppm), and liver (5.62% of TRR, 0.230 ppm); and MB 46400 was also tentatively identified in Day 5 egg yolks (0.99% of TRR, 0.015 ppm), Day 14 egg yolks (5.21% of TRR, 0.375 ppm), and liver (3.26% of TRR, 0.133 ppm). The glucuronide conjugate of MB 46513 was tentatively identified in Day 5 and Day 14 egg yolks (1.42% of TRR, 0.021 ppm, and 6.01% of TRR, 0.432 ppm, respectively), and the sulfate conjugate of MB 46513 was tentatively identified in liver (2.07% of TRR, 0.084 ppm). Three additional metabolites were tentatively identified in liver: ring-opened RPA 105048 (1.76% of TRR, 0.072 ppm), ring-opened RPA 106889 (3.69% of TRR, 0.151 ppm), and the monodechloro, monohydroxy MB 46513 (2.27% of TRR, 0.093 ppm).

In the residue trials, the levels of MB 46513 were <LOQ (0.01 ppm) in all samples. The maximum dietary burden of MB 46513 in ruminants is 0.007 ppm; and in poultry, 0.01 ppm (see below). In the ruminant metabolism study conducted at 10 ppm (1400X), metabolites of MB 46513 were seen only in liver at low levels (2.1-3.4% of the TRR) which correspond to 40-70 **ppt** when normalized to 1X. In the poultry metabolism study conducted at 10 ppm (1000X), metabolites of MB 46513 were seen only in liver and egg yolk at low levels (1.2-6.0% of the TRR) which correspond to 72-430 **ppt** when normalized to 1X. Based on their low levels (both absolute and relative to MB 46513), HED does not consider the metabolites of MB 46513 to be of concern

iv. Residue Analytical Methods

Plants:

In conjunction with the cotton petition, GC/ECD method EC-95-303 has been proposed for enforcement of tolerances for residues of fipronil and its metabolites MB 45950, MB 46136, MB 46513, and RPA 200766 in/on plant commodities. Fipronil and its metabolites are analyzed in a single chromatographic separation. The LOQ for each analyte is 0.003-0.01 ppm depending on the matrix. This method has undergone a successful PMV (DP Barcode D234562, G. Kramer, 4/29/97), and will be suitable for enforcement purposes for fipronil and its metabolites once the revisions recommended by ACL have been incorporated. Note that all directions pertaining to RPA 200766 should also be removed as this metabolite has been determined to not be of regulatory concern. Briefly, samples of rice grain and straw were extracted with ACN:water and vacuum filtered. The filtrates were combined and mixed with ACN:aqueous NaCl, then partitioned with hexane. The aqueous layers following phase separation were

combined, and ACN was removed by rotary evaporation. The remaining aqueous phase was extracted with dichloromethane. Following phase separation, the combined dichloromethane extracts were concentrated by rotary evaporation and cleaned up with column packed with Florisil, acidic alumina, silica gel, activated charcoal, and anhydrous sodium sulfate. Residues were eluted with ACN:methanol and the eluate was concentrated by rotary evaporation and dissolve in ACN prior to GC analysis. GC analyses were conducted using a DB-1701 column and mass selective or electron capture detection (MSD or ECD).

Rice grain samples from the processing study were analyzed using the same method with minor modifications. The final eluate was analyzed by GC/ECD. GC analyses were conducted using a DB-5 column.

The GC methods used for the analyses of samples collected from the rice crop field trials and processing study are adequate for collection of residue data. Adequate method validation and concurrent method recovery have been submitted for these methods. These methods are similar to the GC method proposed for cottonseed which has undergone a successful PMV.

Animals:

A method for the determination of residues of fipronil and its metabolites MB 45950 and MB 46136 in animal commodities was previously reviewed in conjunction with a petition for corn and animal RACs (PP#5F04426; CBTS No. 15436, DP Barcode D214376, G. Kramer, 7/25/95 and CBTS Nos. 16773 and 16774, DP Barcodes D222541 and D222350, G. Kramer, 4/1/96), and has undergone a successful PMV (CBTS No. 16339, DP Barcode D220222, G. Kramer, 10/26/95).

v. Multiresidue Methods

A report on Multiresidue testing of fipronil and its metabolites MB 45950 and MB 46136 (MRID# 434011-07) has been received and forwarded to FDA (Memo, G, Kramer 5/9/95). Acceptable recoveries of fipronil and its metabolites were obtained in corn grain using Protocol E. Recoveries in forage were 38-65% using Protocol E. A report on Multiresidue testing of MB 46513 (MRID# 443748-01) has been received and forwarded to FDA (Memo, S. Chun x/x/97). Acceptable recoveries of MB 46513 were obtained in rice grain using Protocol E and cottonseed using Protocol F. Recoveries were ??-???% using Protocol E and 72-89% using Protocol F.

vi. Storage Stability Data

Samples from the submitted field trials and the processing study were stored frozen for a maximum of 11 months prior to analysis. Storage stability data were previously submitted and reviewed in conjunction with a petition for corn and animal RACs (PP#5F04426; CBTS Nos. 16773 and 16774, DP Barcodes D222541 and D222350, G. Kramer, 4/1/96 and CBTS No. 15436, DP Barcode D214376, G. Kramer, 7/25/95). The data demonstrated that residues of fipronil and its metabolites MB 45950, MB 46136, RPA105048, and RPA200766 are stable under frozen conditions for up to 2 years in/on corn grain, and for 12 months in/on corn forage, fodder, silage, crude oil, refined oil, grain dust, meal, and starch. The available frozen storage stability data support the storage intervals of the submitted field trials; however, data depicting the storage stability of the metabolite MB 46513 in/on rice grain and straw stored frozen for up to 11 months are required. We note that the petitioner had reported that a 1-year freezer stability study for residues of fipronil and its metabolites (which include MB 46513) in cotton commodities was in progress (CBTS No. 16288, D219819, G. Kramer 11/12/96). If the results of this study are acceptable, these data may be adequate to support the rice field trials and processing study.

vii. Crop Field Trials

Rhône-Poulenc has submitted data from 17 crop field trial studies (MRID 44261910 & 44355401) depicting residues of fipronil in/on rice.

Seventeen field trials were conducted in AR(5), CA(3), LA(5), MS(2), and TX(2). A field trial was conducted in MO, but no samples were obtained. At each site rice grain and straw were harvested at normal maturity, 107-143 days following a preplant incorporated (PPI) broadcast application of the 80% WDG formulation at ~0.05 lb ai/A (1x the maximum proposed application rate) or seed treatment with a 10% liquid formulation equivalent to ~0.05 lb ai/A at the stated seeding rate. Trials conducted in MRID44355401 utilized a 56% liquid formulation for both the PPI broadcast application and the seed treatment equivalent to ~0.05 lb. ai/A (1x the maximum proposed application rate).

Preplant incorporated applications were made in 8-21 gal of water/A using ground equipment (CO_2 backpack or tractor-mounted sprayers); seed treatment was made either to dry seed using a laboratory-sized seed treatment apparatus after which seed was air dried for 12 hours, or

to seed which had been soaked with water for 24 hours by mixing the seed in a plastic bag with the fipronil formulation and a polymer additive. Rice seed was planted using normal cultural practices: dry seeding or water seeding (flooding). For the seed treatments, dry seed was used for dry seeding and pre-soaked seed was used for water seeding; the petitioner noted that the use of pre-soaked seed for water seeding is not yet a commercial practice. The total application rates for PPI treatments were 0.047-0.053 lb ai/A and for seed treatments were 0.044-0.052 lb ai/A.

The LOQ for is 0.01 ppm. The method was validated over a range of 0.01-5.0 ppm for rice RACs. The average percent recovery for rice grain was fipronil (94%), MB 45950 (90%), MB 46136 (102%), MB 46513 (98%), and RPA 200766(110%). The average percent recovery for rice straw was fipronil (89%), MB 45950 (88%), MB 46136 (96%), MB 46513 (93%), and RPA 200766 (104%). In the eight field trials submitted separately (MRID # 44355401), no percent recoveries were obtained for RPA 200766.

Residues of fipronil and its four metabolites were each less than the LOQ (<0.010 ppm) in/on 10 samples each of untreated rice grain and straw.

A total of 17 field trials for each formulation and application type were conducted with rice in Regions 4 (12 trials), 6 (2 trial), and 10 (3 trials). The number and location of field trials is not adequate to support the proposed use of the fipronil on rice. One additional trial is required in Region 5.

The submitted data indicate that the combined residues of fipronil, MB 45950, MB 46136, and MB 46513 will not exceed the proposed tolerance for rice straw (0.10 ppm), but could exceed the proposed tolerance for rice grain (0.02 ppm) in/on samples harvested at maturity following either a preplant incorporated (PPI) broadcast application of the 80% WDG formulation or seed treatment with a 10% liquid formulation at ~0.05 lb ai/A (1x the proposed maximum rate). The combined residues in/on rice following the above treatments were less than the combined LOQ (<0.04 ppm) in/on rice grain (34 samples each from PPI and seed treatments), and <0.04-<0.053 ppm in/on rice straw from PPI treatments and <0.04-<0.054 ppm in/on rice straw from seed treatments (34 samples each).

Based on the highest residue value obtained from samples harvested following the proposed PPI or seed treatments at the proposed maximum use rate, the proposed tolerance level of 0.10 ppm for rice

straw is appropriate. The proposed tolerance level of 0.02 ppm for rice grain is too low. Because no residues of fipronil or its metabolites were detected in rice grain, the petitioner should propose a tolerance level for rice grain at the combined limits of quantitation for fipronil and the three metabolites to be included in the tolerance expression. **Pending receipt of the outstanding residue data, a revised Section F should be submitted amending the proposed tolerance for rice grain to 0.04 ppm.**

viii. Processed Food/Feed

Rhône-Poulenc submitted the data (MRID 44261911) depicting the potential for concentration of fipronil residues in the processed commodities of rice.

Two trials were conducted in LA(1) and TX(1). At each site, rice grain was harvested at normal maturity, 110-119 days following a PPI broadcast application of the 80% WDG formulation at ~0.25 lb ai/A (5x the maximum proposed application rate) or seed treatment with a 10% liquid formulation equivalent to ~0.30 lb ai/A at the stated seeding rate (6x the maximum proposed application rate). Preplant incorporated applications were made in 17 and 18 gal/A of water using ground equipment; seed treatment was made to dry seed using seed treatment apparatus. Total application rates for PPI treatments were 0.251 and 0.254 lb ai/A (5x the maximum application rate) and for seed treatments were 0.304 and 0.293 lb ai/A (6x the maximum application rate).

The control and bulk treated samples were collected either mechanically or manually from the designated test plots. Composite samples from the LA and TX sites were shipped to South Texas Ag Research (Brookshire, TX) for processing. Samples were processed according to simulated commercial procedures into hulls, bran, and polished rice.

Apparent residues of fipronil and its metabolites MB 45950, MB 46136, MB 46513, and RPA200766 were each less than the LOQ (<0.01 ppm) in/on two samples each of untreated rice grain and on reanalysis of hydrated samples. Residues were less than the LOQ (<0.01 ppm) in/on two samples each of treated rice grain from the PPI and seed treatments and on reanalysis of hydrated samples. Because quantifiable residues were not obtained from rice grain treated at 5x the maximum proposed application rate, no analyses were performed on the processed samples of hulls, bran, or polished rice.

The submitted rice processing data are adequate. The data indicate that total residues of fipronil and its metabolites MB 45950, MB 46136, MB 46513, and RPA200766 are less than the LOQ (<0.01 ppm) in/on rice grain harvested at maturity following preplant incorporated broadcast application of the 80% WDG formulation at ~0.25 lb ai/A (5x the maximum proposed seasonal rate) or seed treatment with a 10% liquid formulation equivalent to ~0.30 lb ai/A at the stated seeding rate (6x the maximum application rate). Because treatment at 5-6x did not result in quantifiable levels of fipronil residues of concern in rice grain, all further requirements for the processing study are waived, and no tolerances are required for the processed commodities of rice.

ix. Meat, Milk, Poultry, Eggs

Rice grain, straw, hulls, and bran are animal feed items. The available animal metabolism studies suggest that tolerances for animal commodities are required. According to Section F of the current petition, tolerances for meat, milk, eggs, liver, kidney, meat byproducts, and fat were proposed in conjunction with the tolerance petition PP#5F04426 for fipronil use in/on corn. The petitioner stated that these tolerances are adequate to cover the additional uses of fipronil on rice.

Fipronil: The maximum theoretical dietary burden of fipronil to beef and dairy cattle, based on the required tolerances of 0.04 ppm for rice and 0.10 ppm for rice straw, is 0.04 ppm. The maximum theoretical dietary burden of fipronil to poultry, based on the proposed tolerances of 0.04 ppm for rice and 0.10 ppm for rice straw, is 0.04 ppm

Acceptable cow and poultry feeding studies were submitted and reviewed in conjunction with PP#5F04426 (CBTS No. 15436, DP Barcode D214376, G. Kramer, 7/25/95). Based on these studies, the Agency has recommended appropriate tolerance levels for fipronil residues in/on animal commodities (DP Barcode D235683, G. Kramer, 8/11/97). The tolerances for animal commodities established in conjunction with PP#5F04426 are required to support the proposed use on rice.

Based on the expected dietary contribution of fipronil residues in/on eggs, milk, and tissues as the result of the current rice petition and established/proposed tolerances for corn, cotton, and potatoes, the Agency may have to reassess the results of the animal feeding studies to determine the appropriate tolerance levels for animal commodities.

MB 46513: The maximum theoretical dietary burden of MB 46513 to beef and dairy cattle is 0.007 ppm, based on the method LOQ of 0.01 ppm. The maximum theoretical dietary burden of fipronil to poultry, based on the method LOQ of 0.01 ppm, is 0.01 ppm.

In the ruminant metabolism study conducted at 10 ppm (1400X), maximum residues of MB 46513 were seen in fat at levels up to 2.1 ppm, which corresponds to 1.6 ppb when normalized to 1X. In the poultry metabolism study conducted at 10 ppm (1000X), maximum residues of MB 46513 were seen in fat at levels up to 9.7 ppm which correspond to 9.7 **ppb** when normalized to 1X. Based on low potential for residues in meat, milk and eggs, HED will not require animal feeding studies to be conducted with MB 46513.

x. **Water, Fish, and Irrigated Crops** - Not Applicable

xi. **Food Handling** - Not Applicable

xii. **Confined Accumulation in Rotational Crops**

No confined or field rotational crop studies were submitted with this petition. An acceptable confined rotational crop study with radishes, lettuce, grain sorghum, and wheat was submitted and reviewed in conjunction with PP#5F04426 (CBTS Nos. 16773 and 16774, DP Barcodes D222541 and D222350, G. Kramer, 4/1/96; CBTS No. 17402, D228385, G. Kramer, 8/26/96; DP Barcode D235683, G. Kramer, 8/11/97). The results of the study indicate that fipronil is metabolized in rotational crops by: (i) hydrolysis to the amide, RPA 200766, with further hydrolysis to the carboxylic acid, RPA 200761; (ii) oxidation to the sulfone, MB 46136; (iii) desulfurization to MB 46513; or (iv) reduction to MB 45950. Data from the confined rotational crop study support plantback intervals of 1 month for leafy vegetables, 5 months for root crops, and 12 months for small grains and all other crops. The petitioner has reported that limited rotational crop field trials are in progress.

xiii. **Field Accumulation in Rotational Crops** - Not Applicable

xiv. **Tolerance Reassessment Table** - Not Applicable

xv. **Anticipated Residues**

Table 4. Summary of Fipronil Anticipated Residues for Dietary Risk Assessment (Chronic Endpoints) based on field-trial data. The anticipated market share was supplied by BEAD.

Commodity	Recommended Tolerance (ppm)	Anticipated Residue in RAC (ppm)	Anticipated Market Share (%)	Anticipated Residue for DRES Run (ppm)
Corn Grain[1] **Includes processed commodities**	0.02	0.015	7	0.0010
Corn Forage	0.15	0.035	7	0.0024
Corn Stover	0.30	0.061	7	0.0043
Rice Grain[4] **Includes processed commodities Excludes wild rice**	0.03	0.015	11	0.0016
Meat	0.04	0.0005	--	0.0005[3]
Liver	0.10	0.0016		0.0016[3]
Meat by-products (except liver)	0.04	0.0004		0.0004[3]
Fat	0.40	0.005		0.005[3]
Milk Fat[2]	1.50	0.011		0.011
Hog Meat	0.01	0.00014	--	0.00014
Hog Liver	0.02	0.00042		0.00042
Hog Meat by-products (except liver)	0.01	0.00011		0.00011
Hog Fat	0.04	0.0013		0.0013
Poultry meat	0.02	0.00018	--	0.00018
Poultry meat by-products	0.02	0.00074		0.00074
Poultry fat	0.05	0.0018		0.0018
Eggs	0.03	0.0011		0.0011

1 Since residues do not concentrate in processed commodities of corn, the anticipated residue of 0.001 ppm should be used for such commodities in the DRES run (i.e. corn oil, meal, etc.) except corn sugar for which processing data are not available.

2 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

3 These anticipated residues should also be used for meat, fat and meat by-products of horses, goats and sheep in the DRES run.

4 Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.0016 ppm should be used for such commodities in the DRES run (i.e. flour, etc.).

For acute dietary risk assessment, anticipated residues in blended commodities (such as corn and rice processed commodities) may be used, without the adjustment for percent crop treated; however, tolerance level residues should be used for fat, meat by-products and meat of cattle, goats, hogs, horses, sheep and poultry; and eggs [milk is a blended commodity, and therefore an anticipated residue value may be used].

Table 5. Summary of Fipronil Residues for Acute Dietary Risk Assessment

Commodity	Recommended Tolerance (ppm)	Residue to Use in Acute DRES Run (ppm)
Corn Grain[1] **Includes processed commodities**	0.02	0.015
Rice Grain[4] **Includes processed commodities** **Excludes wild rice**	0.04	0.02
Meat	0.04	0.04[3]
Liver	0.10	0.10[3]
Meat by-products (except liver)	0.04	0.04[3]
Fat	0.40	0.40[3]
Milk Fat[2]	1.50	0.16
Hog Meat	0.01	0.01
Hog Liver	0.02	0.02
Hog Meat by-products (except liver)	0.01	0.01
Hog Fat	0.04	0.04
Poultry meat	0.02	0.02
Poultry meat by-products	0.02	0.02
Poultry fat	0.05	0.05
Eggs	0.03	0.03

1 Since residues do not concentrate in processed commodities of corn, the anticipated residue of 0.015 ppm should be used for such commodities in the DRES run (i.e. corn oil, meal, etc.).

2 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

3 These anticipated residues should also be used for meat, fat and meat by-products of horses, goats and sheep in the DRES run.

4 Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.02 ppm should be used for such commodities in the DRES run (i.e. flour, etc.).

Note: As MB 46513 does not appear to be more acutely toxic than the parent, it will be incorporated into the acute DRES run for rice. If further refinements in the acute dietary risk assessment are required in the future, a separate DRES run for MB 46513 only will be performed.

Table 6. Summary of MB 46513 Anticipated Residues for Dietary Risk Assessment

Commodity	Residue to Use in Chronic DRES Run (ppm)
Rice Grain[1] **Includes processed commodities** **Excludes wild rice**	0.0006
Meat	0.0000039
Liver	0.000051
Meat by-products (except liver)	0.0000071
Fat	0.000062
Milk Fat[2]	0.00032
Hog Meat	0.0000051
Hog Liver	0.000067
Hog Meat by-products (except liver)	0.0000094
Hog Fat	0.000082
Poultry meat	0.000012
Poultry meat by-products	0.000082
Poultry fat	0.000019
Eggs	0.00029

1 Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.005 ppm should be used for such commodities in the DRES run (i.e. flour, etc.).

2 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

3 These anticipated residues should also be used for meat, fat and meat by-products of horses, goats and sheep in the DRES run.

(a) Corn and Rice RACs

For samples with residue levels below the LOQ (0.01 ppm in corn grain and rice grain and 0.02 ppm in forage and stover), a value of ½ LOQ used in calculating average residues. In corn grain, the average levels of fipronil were 0.005 ppm; of MB 45950, were 0.005 ppm; and of MB 46136, were 0.005 ppm. In forage, the average levels of fipronil were 0.013 ppm; of MB 45950, were 0.01 ppm; and of MB 46136, were 0.012 ppm. In stover, the average levels of fipronil were 0.011 ppm; of MB 45950, were 0.01 ppm; and of MB 46136, were 0.023 ppm. The samples from the corn residue studies were analyzed with the original version of the proposed enforcement method. This method has been revised by addition of water to the initial extraction solvent for dry matrices (fodder and grain). This revision was found to result is significantly higher residues in fodder samples (Memo, G. Kramer 4/1/96). Fipronil levels were increased by 45%; and MB 46136, by 52%. When applying these correction factors to the fodder residues, the average levels of fipronil were 0.016 ppm; and of MB 46136, were 0.035 ppm. The total anticipated residues of fipronil and

its metabolites are thus 0.015 ppm in corn grain, 0.035 ppm in forage and 0.061 ppm in stover. In rice grain and rice straw, the average levels of fipronil were 0.005 ppm; of MB 46513, were 0.005 ppm; of MB 45950, were 0.005 ppm; and of MB 46136, were 0.007 ppm.

(b) Meat, Milk & Eggs

(I) Fipronil + MB 46136 + MB 45950

Table 7. Anticipated Dietary Burden for Beef and Dairy Cattle

Feed Item	Average AR/%DM[1]	% in Diet[2]		Anticipated Dietary Burden[3]	
		Beef	Dairy	Beef	Dairy
Corn Grain	0.001	60	40	0.0006	0.0004
Corn Forage	0.006	40	50	0.0024	0.0031
			Total:	**0.0030**	**0.0035**

1 Average AR/%DM = average of anticipated residues in feed items divided by the % dry matter (%DM) for the feed item. %DM: 88% for corn grain and 40% for forage. **Note: The ARs incorporate projected market share (7%).**

2 The % of each feed type assumed to be included in the diet was based on information contained in the revised Table I of the OPPTS Test Guidelines Series 860.

3 The anticipated dietary burden is calculated by multiplying the average AR/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant feeding study correspond to 13X, 43X and 143X the anticipated dietary burden for beef cattle (0.0030 ppm, Table 7) and 11X, 37X and 123X the anticipated dietary burden for dairy cattle (0.0035 ppm, Table 7). Based on this information, and based on the residues found in meat, meat by-products, fat and milk in the ruminant feeding study, the anticipated residues in livestock commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.0005 ppm
liver	0.0016 ppm
meat by-products (except liver)	0.0004 ppm
fat	0.0050 ppm
milk fat	0.011 ppm

Note: The milk fat residue is based on the average residues in whole milk (0.042 ppm, after plateauing) found in the 0.43 ppm dose group multiplied by a concentration factor of 31X.

Table 8. Anticipated Dietary Burden for Poultry and Swine

Feed Item	Average AR/%DM[1]	% in Diet[2]		Anticipated Dietary Burden[3]	
		Poultry	Swine	Poultry	Swine
Corn Grain	0.001	80	80	0.0008	0.0008

1 Average AR/%DM = average of anticipated residues in feed items divided by the % dry matter (%DM) for the feed item. %DM: 88% for corn grain. A dry matter correction was not performed for poultry. **Note: The ARs incorporate projected market share (7%).**

2 The % of each feed type assumed to be included in the diet was based on information contained in the revised Table I of the OPPTS Test Guidelines Series 860.

3 The anticipated dietary burden is calculated by multiplying the average AR/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant feeding study correspond to 50X, 162X and 540X the anticipated dietary burden for swine (0.0008 ppm, Table 8). Based on this information, and based on the residues found in meat, meat by-products, and fat in the ruminant feeding study, the anticipated residues in swine commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.00014 ppm
liver	0.00042 ppm
meat by-products (except liver)	0.00011 ppm
fat	0.0013 ppm

The dosing levels used in the poultry feeding study correspond to 12X, 39X and 129X the anticipated dietary burden for poultry (0.0008 ppm, Table 8). Based on this information, and based on the residues found in meat, liver, eggs, and fat in the poultry feeding study, the anticipated residues in poultry commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.00018 ppm
eggs	0.0011 ppm
meat by-products	0.00074 ppm
fat	0.0018 ppm

(ii) MB 46513- CHRONIC

Table 9. Anticipated Dietary Burden for Beef and Dairy Cattle

Feed Item	Average AR/%DM[1]	% in Diet[2]		Anticipated Dietary Burden[3]	
		Beef	Dairy	Beef	Dairy

Rice grain	0.0006	40	40	0.00025	0.00025
Rice straw	0.0006	10	10	0.00006	0.00006
			Total:	**0.00031**	**0.00031**

1 Average AR/%DM = average of anticipated residues in feed items divided by the % dry matter (%DM) for the feed item. %DM: 88% for rice grain and 90% for straw. **Note: The ARs incorporate projected market share (11%).**

2 The % of each feed type assumed to be included in the diet was based on information contained in the revised Table I of the OPPTS Test Guidelines Series 860.

3 The anticipated dietary burden is calculated by multiplying the average AR/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant metabolism study correspond to 32,000X the anticipated dietary burden for beef and dairy cattle (0.00031 ppm, Table 9). Based on this information, and based on the residues found in meat, meat by-products, fat and milk in this study, the anticipated residues in livestock commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.0000039 ppm
liver	0.000051 ppm
meat by-products (except liver)	0.0000071 ppm
fat	0.000062 ppm
milk fat	0.00032 ppm

Note: The milk fat residue is based on thee residues in whole milk (0.337 ppm) multiplied by a concentration factor of 31X.

Table 10. Anticipated Dietary Burden for Poultry and Swine.

Feed Item	Average AR/%DM[1]	% in Diet[2]		Anticipated Dietary Burden[3]	
		Poultry	Swine	Poultry	Swine
Rice grain	0.0006	60	65	0.00033	0.00041

1 Average AR/%DM = average of anticipated residues in feed items divided by the % dry matter (%DM) for the feed item. %DM: 88% for rice grain. A dry matter correction was not performed for poultry. **Note: The ARs incorporate projected market share (11%).**

2 The % of each feed type assumed to be included in the diet was based on information contained in the revised Table I of the OPPTS Test Guidelines Series 860.

3 The anticipated dietary burden is calculated by multiplying the average AR/%DM by the % of the feed item in the diet.

The dosing levels used in the ruminant metabolism study correspond to 24,000X the anticipated dietary burden for swine (0.00041 ppm, Table 10). Based on this information, and based

on the residues found in meat, meat by-products, and fat in the ruminant metabolism study, the anticipated residues in swine commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.0000051 ppm
liver	0.000067 ppm
meat by-products (except liver)	0.0000094 ppm
fat	0.000082 ppm

The dosing level used in the poultry metabolism study corresponds to 30,000X the anticipated dietary burden for poultry (0.00033 ppm, Table 10). Based on this information, and based on the residues found in meat, liver, eggs, and fat in the poultry metabolism study, the anticipated residues in poultry commodities to be used in the chronic dietary risk assessments are shown below:

meat	0.000012 ppm
liver	0.000082 ppm
meat by-products	0.000019 ppm
fat	0.00029 ppm

b. Dietary Exposure (Drinking Water Source)

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for fipronil at this time. The Environmental Fate and Effects Division (EFED) provided ground and surface water exposure estimates for use on corn (RED, GML, 11/20/97). The data from corn is being used because fipronil is applied at a higher use rate on corn than rice and thereby providing more conservative estimates.

I. Ground Water (tiered assessment)

The environmental fate data for fipronil indicate a moderate to high persistence and relatively low mobility in terrestrial environments. Based on the SCI-GRO model, acute drinking water concentration in shallow ground water on highly vulnerable sites are not likely to exceed the following:

	ppb
Fipronil	0.055
MB 46136	0.001
MB 45950	0.00036
Total:	0.05636

	ppb
MB 46513	0.00026

Chronic concentrations are not expected to be higher than acute values. Highly vulnerable sites are those with low organic matter, coarse textured soils (e.g., sands and loamy sands) and shallow ground water. The fate data for fipronil and its degradates indicate a higher potential mobility on coarse-textured soils (sand or loamy sands).

ii. Surface Water (tiered assessment)

Based on the environmental fate assessment, fipronil and its degradates (MB 46513, MB 46136, and MB 45950) can potentially move into surface waters. Since fipronil is used as an in-furrow application on field corn, the runoff potential of fipronil residues is expected to be lower than for unincorporated surface application techniques. Since photodegradation is a major route of degradation for fipronil, its dissipation is expected to be dependent on physical components of the water (i.e. sediment loading) which affect sunlight penetration. The maximum fipronil concentration for acute (peak concentration) and chronic (56-day average) based on the Tier 1 GENEEC surface water modeling is shown in Table 11 below.

Table 11 - Surface water concentrations for Fipronil based on GENEEC modeling

	Acute Peak EEC (ppb)	Chronic 56-day EEC (ppb)
Fipronil	2.05	0.78
MB 46136	0.168	0.062
MB 45950	0.039	0.019
Total:	2.257	0.861

Table 12 - Surface water concentrations for MB 46513 based on GENEEC modeling

	Acute Peak EEC (ppb)	Chronic 56-day EEC (ppb)
MB 46513	0.014	0.009

c. Dietary Risk Assessment and Characterization

I. Chronic Risk (TMRC, ARC)

A chronic dietary risk assessment is required for fipronil (+ MB 46136 and MB 4595). The RfD used for the chronic dietary analysis for parent fipronil and 2 metabolites is 0.0002 mg/kg bwt/day. The RfD used for the metabolite MB 46513 is 0.00002 mg/kg bwt/day.

Chronic dietary exposure estimates (DRES) for fipronil (+ 2 metabolites) and MB 46513 are summarized in Attachment **2** (runs dated 12/5/97). The DRES analysis utilized the anticipated residues calculated from field-trial data for all rice, corn and animal commodities. The proposed fipronil tolerances result in an Anticipated Residue Contribution (ARC) that is equivalent to the following percent of the RfD:

Subgroups	Fipronil	MB 46513	Total
U.S. Population (48 states)	4.8%	1.7%	6.5%
Hispanics	6.2%	2.9%	8.1%
Non-Hispanic Others	5.8%	3.9%	9.7%
Nursing Infants (< 1 year old)	2.8%	2.3%	5.1%
Non-Nursing Infants (< 1 year old)	11.2%	5.5%	16.7%
Females (13+ years, pregnant)	3.3%	1.2%	4.5%
Females (13+ years, nursing)	4.2%	1.6%	5.8%
Children (1-6 years old)	11.4%	3.8%	15.2%
Children (7-12 years old)	7.6%	2.3%	9.9%
Females (20+ years, not pregnant, not nursing)	3.0%	1.2%	4.2%

HED does not consider the chronic dietary risk to exceed the level of concern.

ii. Carcinogenic Risk

Fipronil + MB 46136 + MB 45950

Dietary risk concerns due to long-term consumption of fipronil residues are adequately addressed by the DRES chronic exposure analysis using the RfD.

MB 46513

Dietary risk concerns due to long-term consumption of MB 46513 residues are adequately addressed by the DRES chronic exposure analysis using the RfD.

iii. Acute Dietary Risk

An acute dietary risk assessment is required for fipronil and MB 46513. The NOEL of 0.5 mg/kg/day was selected as the endpoint to be used for fipronil and all its metabolites (Note: 2 mg/kg/day was the endpoint selected for MB 46513 for acute dietary risk assessments) Since the metabolite MB 46513 does not appear to be more acutely toxic than the parent, it will be incorporated into the acute DRES run for rice. If further refinements in the acute dietary risk assessment are required in the future, a separate DRES run for MB 46513 only will be performed. HED's detailed acute analysis estimate the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as resorted by respondents in the USDA 1977-78 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of fipronil in the commodity supply.

The MOE is a measure of how closely the anticipated exposure comes to the NOEL and is calculated as a ration of the NOEL to the exposure.

$$\frac{NOEL}{exposure} = MOE$$

The Agency is not generally concerned unless the MOE is below 100 when the NOEL is based upon data generated in animal studies. The 100 accounts for the interspecies extrapolation and intraspecies variability.

Table 13 - Acute Risk for Fipronil and all Metabolites

Subgroup	NOEL (mg/kg/day)	Exposure (mg/kg/day)	MOE*
General U.S. Population	0.5	0.0018	278
Infants (< 1 year)	0.5	0.003	167
Children (1-6 years)	0.5	0.003	167
Females (13+ years)	0.5	0.0012	417
Males (13+ years)	0.5	0.0014	357

iv. Drinking Water Risk (Acute and Chronic)

Fipronil [+ MB 45950, MB 456136, and MB 46513(acute only)]

OPP has calculated drinking water levels of concern (DWLOCs) for acute exposure to fipronil (plus MB 45950 , MB 46136, and MB 46513) in surface and ground water for the U.S. population and children (1-6 yrs). They are **112** and **20 ppb**, respectively. For chronic (non-cancer) exposure to fipronil (plus MB 45950 and MB 46136) in surface and ground water, the drinking water levels of concern are **6.67** and **1.77 ppb** for U.S. population, children (1-6 years old), respectively. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DRES analysis) was subtracted from the ratio of the acute NOEL (used for acute dietary assessments) to the "acceptable" MOE for aggregate exposure to obtain the acceptable acute exposure to fipronil (plus MB 45950 , MB 46136 and MB 46513) in drinking water. To calculate the DWLOC for chronic (non-cancer, cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to fipronil (plus MB 45950 and MB 46136) in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures.

Estimated maximum concentrations of fipronil (plus MB 45950, MB 46136, and MB 46513) in surface and ground water are **2.271** and **0.05662 ppb** (with 0.00026 ppb from MB 46513 included), respectively. The estimated average concentration of fipronil (plus MB 45950 and MB 46136) in surface water is **0.861 ppb**. Chronic concentrations in ground water are not expected to be higher than the acute concentrations. *Note: For the purposes of the screening-level*

assessment, the maximum and average concentrations in ground water are not believed to vary significantly. The maximum estimated concentrations of fipronil (plus MB 45950 and MB 46136) in surface and ground water are less than OPP's levels of concern for fipronil (plus MB 45950 and MB 46136) in drinking water as a contribution to acute aggregate exposure. The estimated average concentrations of fipronil (plus MB 45950 and MB 46136) in surface and ground water are less than OPP's levels of concern for fipronil (plus MB 45950 and MB 46136) in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of fipronil (plus MB 45950 and MB 46136) in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of fipronil (plus MB 45950 and MB 46136) in surface waters and ground waters to back-calculated "levels of concern" for fipronil (plus MB 45950 and MB 46136) in drinking water. These levels of concern in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of fipronil (plus MB 45950 and MB 46136) in surface and ground waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of fipronil (plus MB 45950 and MB 46136) on drinking water as a part of the aggregate risk assessment process.

MB 46513 (chronic only)

For chronic (non-cancer) exposure to MB 46513 in surface and ground water, the drinking water levels of concern are **0.69** and **0.19 ppb** for U.S. population, children (non-nursing infants, < 1 year old), respectively. To calculate the DWLOC for chronic (non-cancer, cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DRES) was subtracted from the RfD to obtain the acceptable chronic (non-cancer) exposure to MB 46513 in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures.

Estimated maximum concentrations of MB 46513 in ground water is **0.00026 ppb**. The estimated average concentration of MB 46513 in surface water is **0.009 ppb**. Chronic concentrations in ground water are not expected to be higher than the acute concentrations. *Note: For the purposes of the screening-level assessment, the maximum and average concentrations in ground water are not believed to vary significantly.* The estimated average concentrations of MB 46513 in surface and ground water are less than OPP's levels of concern for MB 46513 in drinking water as a contribution to chronic aggregate exposure. Therefore, taking into account the present uses and uses proposed in this action, OPP concludes with reasonable certainty that residues of MB 46513 in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time.

OPP bases this determination on a comparison of estimated concentrations of MB 46513 in surface waters and ground waters to back-calculated "levels of concern" for MB 46513 in drinking water. These levels of concern in drinking water were determined after OPP has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of MB 46513 in surface and ground waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of MB 46513 on drinking water as a part of the aggregate risk assessment process.

d. Statement of the adequacy of the dietary exposure database to assess infants' and children's exposure

The dietary (food and water) exposure database for fipronil is adequate to assess infants' and children's exposure.

4. Occupational and Residential Exposure and Risk Assessment/Characterization

a. Occupational and Residential Exposure

I. Summary of Use Patterns and Formulations: Occupation and Residential

The information in Table 14, below is taken from Icon 6.2 FS, Icon 80 WG, Icon 6.2 SC, and other sources as cited.

Table 14. Registration Request for Use of Icon (6.2 FS, 80 WG, and 6.2 SC) in/on rice.

Factors	Comments
Crop to be treated	Rice
Pests	In furrow, preplant incorporated, or as a seed treatment to control rice weevil and chinch bugs.
Application methods	Aerial, and groundboom application or as a seed treatment (SC formulation only).
Maximum application rate	Regardless of formulation: 0.025 to 0.05 lbs ai/A.
Maximum number of applications	One application at planting.
Percent Absorption	Endpoint is derived from a dermal study. Therefore, adjustment for dermal absorption is not necessary.
Average Acreage of Application per Day	**Aerial** - 480, and **Ground boom** - 80 acres[1]
Manufacturer	Rhône Poulenc Ag Company.

[1] The estimate of maximum acreage used in this assessment of worker exposure is representative of the maximum standard acreage for Aerial and Ground boom on rice.

Acute toxicity endpoints are established for the active ingredient for short-term, intermediate-term, and chronic occupational or residential exposure. The short- and intermediate-term endpoints are derived from a 21 day dermal toxicity study in rabbits. The NOEL is 5 mg/kg/day and the LOEL was 10 mg/kg/day based on decreased body weight gain and food consumption. For acute oral (non-dietary) a NOEL of 2.5 mg/kg/day was selected from an acute neurotoxicity study in rats. The LOEL of 5 mg/kg/day was based on reduced hind limb splay.

Risk assessments are required for short-term, intermediate-term, and chronic exposure, where appropriate. This active ingredient will not be used over several months, hence a chronic exposure assessment is not required.

Because of the potential for exposure via inhalation, an component for this route has been included in the following estimates of exposure for workers wearing a respirator as required on current labeling.

TYPE OF TOXICITY	TOXICITY CATEGORY	
	Active ingredient	Icon 6.2 FS
Acute Oral	III	II
Acute Dermal	III	III
Acute Inhalation	II	I*
Primary Eye	III	III
Primary Dermal	IV	III
Dermal Sensitization	non-sensitizing	non-sensitizing

* Assume I, study was unacceptable

ii. Handler Exposures and Assumptions

HED's exposure assessment is based on the assumptions in Table 15.

Table 15. Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Applicator body weight	70 kg
Mixer/loader body weight	70 kg
Application rate (Seed Treatment Aerial and Groundboom)	0.025 - 0.05 lb ai/A
Acres treated per day (Aerial) Acres treated per day (Groundboom) Acres planted per day (grain drill)	480 acres 80 acres 40 acres[1]
Applicator unit exposure from PHED (Aerial application; liquid; closed cab; with long-pants, long-sleeved shirt, and no gloves).	Dermal - 5.0 µg/lb ai handled[2] Inhalation - 0.1 µg/lb ai handled[2]
Applicator unit exposure from PHED (Groundboom application; liquid; open cab; with coveralls over short-pants, short-sleeved shirt, and gloves). Inhalation assumes the use of a respirator.	11.0 µg/lb ai handled[2] Inhalation - 0.1 µg/lb ai handled[2]
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of Aerial and Groundboom application; liquid; open mixing; with coveralls over short pants, short-sleeved shirt, and gloves). Inhalation assumes the use a respirator.	Dermal - 18.0 µg/lb ai handled[3] Inhalation - 0.1 µg/lb ai handled[3]
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), (In support of Groundboom application; dry flowable; open mixing; with coveralls over short pants, short-sleeved shirt, and gloves). Inhalation assumes the use of a respirator.	Dermal - 48.0 µg/lb ai handled[4] Inhalation - 0.1 µg/lb ai handled[4]
Mixer/loader unit exposure from the Pesticide Handlers Exposure Database (PHED), Loading treated seed in to grain drills and aircraft using open mixing/loading; assuming loading treated seed is similar to loading granular formulations. (Long sleeved shirt, long pants, no gloves and no respirator).	Dermal - 8.4 µg/lb ai handled[5] Inhalation - 1.7 µg/lb ai handled[5]
Personal protective equipment (PPE), per label.	**For all labels:** Coveralls over short-sleeved shirt and short pants; chemical-resistant gloves and respirators.

[1] Standard assumptions of the acreage treated per day given the crop (rice), application method and ground speed.

[2] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): for applicators (Aerial, pg 36; Groundboom, pg 27), liquid, closed cab (aerial)/open cab (groundboom), long pants, long sleeves, no gloves (aerial)/gloves (groundboom). These unit exposures were adjusted to reflect coveralls over short pants and short sleeved shirt (50%) except for aerial applicators.

[3] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): page 19, for mixer/loaders, Aerial & Groundboom, liquid, open mixing, with, long pants, long sleeves, gloves. These unit exposures were adjusted to reflect coveralls over short pants and short sleeved shirt (50%).

[4] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): for

mixer/loaders, Aerial & Groundboom, dry flowable, long pants, long sleeves, gloves. These unit exposures were adjusted to reflect coveralls over short pants and short sleeved shirt (50%).

[5] Source: Pesticide Handlers Exposure Database V1.1, Surrogate Exposure Guide (May 97): for mixer/loaders, Aerial & Groundboom, dry flowable, long pants, long sleeves, gloves. These unit exposures were adjusted to reflect coveralls over short pants and short sleeved shirt (50%).

iii. Post-Application Exposures and Assumptions: Occupational and Residential

(a) Occupational

Rice is harvested mechanically resulting in low postapplication exposure. Postapplication exposure is also mitigated via soil incorporation as required after the application of fipronil. The photodegradate (MB46513) is not expected to play a significant role in postapplication exposure since fipronil is soil incorporated. Its behavior in aquatic environments following field flooding is not known to HED.

(b) Residential

The residential uses of fipronil include the use of ant and cockroach bait traps ranging from 0.01 to 0.05 percent active ingredient. This chemical is also used by homeowners to treat cats and dogs as a pump spray (0.29% RTU) and by applying a small line of 9.7% RTU along the back of the animal. The flea and tick spray use scenario is expected to result in the highest exposure of fipronil products. Based on the high MOE's resulting from these uses (see below), the application of small amounts along the topline of the pet was not addressed. This use is expected to result in much lower exposure based on lower duration and a considerably smaller area being treated. Exposure from the use of fipronil in self contained bait stations is also expected to result in lower exposures since there is no contact with the pesticide.

Based upon a review of the toxicology database for fipronil, a risk assessment is required for acute, short-term, and intermediate-term residential exposure. The endpoint selected for non-occupational exposure assessments is based on the results of a 21-day dermal toxicity study (the systemic toxicity **NOEL was 5.0 mg/kg/day**, based on decreased body weight gain and food consumption in male and female rabbits observed at 10 mg/kg/day). In addition, for incidental non-dietary (acute) exposures, the endpoint selected for acute dietary (oral) assessments is being used. The NOEL was 0.5 mg/kg/day in an acute neurotoxicity study in rats, based on decreased hind leg splay in

male and female rats observed at 5 mg/kg.

Applications of fipronil as a flea and tick spray are expected to occur several times per year in residential settings, resulting in acute and short- and intermediate-term exposures. This conclusion is based on label directions suggesting retreatment be conducted every 1 to 3 months. Fipronil is reportedly strongly bound to the skin and does not come off the dog once dry. Therefore, the use of fipronil products in residential situations is not expected to result in chronic exposures. It should be noted that an exposure study assessing exposures resulting from the pet uses will be submitted in the Fall of 1997.

The Margin of Exposure (MOE) for applicators of the 0.29% ready-to-use formulation on dogs and cats is 50,000.

The MOE for a child/dermal contact with a wet or recently treated pet is 1000 to 2000.

The MOE for a child/hand-to-mouth exposure after petting a wet or recently treated pet is 5000 to 8000.

See Attachment IV for additional information.

iv. Mixer/Loader/Application Exposure Assessment Formulas and Exposure Tables

Table 16, 17, 18 below, summarizes the HED/RAB1 estimates for total worker exposure for applicators and mixer/loaders in the proposed use of fipronil, on rice. These estimates are based on the assumptions outlined in Table 15.

Table 16. Worker Exposure to Icon 80 WG Insecticide

Job Function	Average Dermal Daily Dose for Icon 80 WG mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Mixer/loaders	Aerial - 0.01 - 0.02 Groundboom - 0.001 - 0.003	Aerial - 250 - 500 Groundboom - 1,667 - 5,000
Applicators	Aerial - 0.001 - 0.002 Groundboom -0.0003 - 0.0006	Aerial - 2,500 - 5,000 Groundboom - 8333 - 16,667

MOE = NOEL/ADD (where NOEL = 5 mg/kg/day)

The exposure estimates in Table 7a are based on treatment of 480 acres per day by aerial and 80 acres per day by ground boom.
The following calculations were used to determine the expected worker exposures resulting from the handling and application of Fipronil (Icon 80 WG) to rice.

Table 17. Worker Exposure to Icon 6.2 SC Insecticide

Job Function	Average Dermal Daily Dose for Icon 6.2 SC mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Mixer/loaders	Aerial - 0.003 - 0.006 Groundboom -0.0005 - 0.001	Aerial - 833 - 1,667 Groundboom - 5,000 - 10,000
Applicators	Aerial- 0.001 - 0.002 Groundboom -0.0003 - 0.0006	Aerial - 2,500 - 5,000 Groundboom - 8,333 - 16,667

MOE = NOEL/ADD (where NOEL = 5 mg/kg/day)

The exposure estimates in Table 7b are based on treatment of 480 acres per day by aerial and 80 acres per day by ground boom.
The following calculations were used to determine the expected worker exposures resulting from the handling and application of fipronil to rice.

Table 18. Worker Exposure to Icon 6.2 FS Insecticide

Job Function	Average Dermal Daily Dose for Icon 6.2 FS mg ai/kg bw/day	Dermal Short & Intermediate-Term MOE
Mixer/loaders	Aerial - 0.01 - 0.02 Groundboom -0.001 - 0.003	Aerial - 250 - 500 Groundboom - 1,667 - 5000
Applicators	Aerial - 0.001 - 0.002 Groundboom -0.0003 - 0.0006	Aerial - 2500 - 5000 Groundboom - 4167 - 8333
Loading treated seed	Aerial - 0.001 - 0.003 Grain drill -0.0001 - 0.0002	Aerial - 1667 - 5000 Grain drill - 25,000 - 50,000

MOE = NOEL/ADD (where NOEL = 5 mg/kg/day)

The exposure estimates in Table 7b are based on treatment of 480 acres per day by aerial and 80 acres per day by ground boom. It is expected that a grower can plant 40 acres per day using a grain drill. Aircraft are expected to plant 480 acres per day. The following calculations were used to determine the expected worker exposures resulting from the handling and application of fipronil to rice.

Mixer Loader

Icon 6.2 FS and 80 WG

Groundboom

0.05 *lbs. ai applied/acre* × 80 *of acres treated/day* = 4 *lbs ai/day*

.048 *mg/lb ai handled (PHED, Version* 1.1) × 4 *lbs ai/day* = 0.192 *mg ai/day*

$$\frac{0.192 \text{ mg ai/day}}{70 \text{ kg bw}} = 0.003 \text{ mg ai/kg bw/day}$$

Aircraft

0.05 *lbs. ai applied/acre* × 480 *of acres treated/day* = 24 *lbs ai/day*

.048 *mg/lb ai handled (PHED, Version* 1.1) × 24 *lbs ai/day* = 1.152 *mg ai/day*

$$\frac{1.152 \text{ mg ai/day}}{70 \text{ kg bw}} = 0.016 \text{ mg ai/kg bw/day}$$

Icon 6.2 SC

Groundboom

0.05 *lbs. ai applied/acre* × 80 *of acres treated/day* = 4 *lbs ai/day*

0.018 *mg/lb ai handled (PHED, Version* 1.1) × 4 *lbs ai/day* = 0.072 *mg ai/day*

$$\frac{0.072 \text{ mg ai/day}}{70 \text{ kg bw}} = 0.001 \text{ mg ai/kg bw/day}$$

Aircraft

0.05 *lbs. ai applied/acre* × 480 *of acres treated/day* = 24 *lbs ai/day*

0.018 *mg/lb ai handled (PHED, Version* 1.1) × 24 *lbs ai/day* = 0.432 *mg ai/day*

$$\frac{0.432 \text{ mg ai/day}}{70 \text{ kg bw}} = 0.006 \text{ mg ai/kg bw/day}$$

Icon 6.2 FS, Icon 6.2 SC, and 80 WG

Spray

Groundboom

0.05 *lbs. ai applied/acre* × 80 *of acres treated/day* = 4 *lbs ai/day*

0.011 *mg/lb ai handled (PHED, Version* 1.1) × 4 *lbs ai/day* = 0.044 *mg ai/day*

$$\frac{0.044 \text{ mg ai/day}}{70 \text{ kg bw}} = 0.0006 \text{ mg ai/kg bw/day}$$

Aircraft

$$0.05\ lbs.\ ai\ applied/acre \times 480\ of\ acres\ treated/day = 24\ lbs\ ai/day$$

$$0.005\ mg/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 24\ lbs\ ai/day = 0.12\ mg\ ai/day$$

$$\frac{0.12\ mg\ ai/day}{70\ kg\ bw} = 0.0017\ mg\ ai/kg\ bw/day$$

Note: For granular which is for the FS formulation only which has seed treatments this subset deals with the loading of treated seed only. The actual seed treatment process is a data gap not unique to this chemical.

Pouring treated seed

Grain drill

$$0.05\ lbs.\ ai\ applied/acre \times 40\ of\ acres\ treated/day = 2\ lbs\ ai/day$$

$$0.0084\ mg/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 24\ lbs\ ai/day = 0.0168\ mg\ ai/day$$

$$\frac{0.0168\ mg\ ai/day}{70\ kg\ bw} = 0.0002\ mg\ ai/kg\ bw/day$$

Flying the Seed On

$$0.05\ lbs.\ ai\ applied/acre \times 480\ of\ acres\ treated/day = 24\ lbs\ ai/day$$

$$0.0084\ mg/lb\ ai\ handled\ (PHED,\ Version\ 1.1) \times 24\ lbs\ ai/day = 0.2016\ mg\ ai/day$$

$$\frac{0.2016\ mg\ ai/day}{70\ kg\ bw} = 0.003\ mg\ ai/kg\ bw/day$$

v. Post-Application Exposure Assessment

The petitioner did not provide post-application exposure sampling data. However, postapplication exposure is mitigated by the fact that it is soil incorporated at planting and the crop is harvested mechanically.

b. Occupation and Residential Risk Assessment/Characterization

I. Risk from Dermal and Inhalation Exposures Equations and Tables

The Agency does not generally have an occupational or residential concern unless MOEs are below 100 when the NOEL is based upon

data generated in animal studies. The 100 accounts for interspecies extrapolation and intraspecies variability. FFDCA section 408 provides that EPA shall apply an additional 10-fold margin of safety for infants and children in the case of threshold effects to account for pre-and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. The additional 10X is not necessary for fipronil (per Hazard I.D. Comm.) due to no increased sensitivity to fetuses (rats and rabbits) and pups (rats); therefore, HED's level of concern for fipronil are for MOEs that are below 100.

Chronic exposure is not expected for use of fipronil on rice, hence a chronic risk assessment will not be done. Also, the Hazard I.D. committee does not consider workers to be at risk from inhalation exposure due to the low toxicity of the chemical. Consequently, an inhalation worker risk assessment will not be done. However unit exposure are presented in table 6 showing inhalation exposures are likely to be much lower than dermal exposure.

ii. Risk from Post-Application Exposures

The default dermal toxicity REI is 24 hours. Due to the fact that the product is soil incorporated at planting, postapplication exposure is not expected. (Assumes that the tox category is II based on the handler PPE which is coveralls over short pants and short sleeved shirt.

iii. Restricted Entry Interval (REI)

Based on the Tox Category, the appropriate REI is 24 hours.

iv. Incident Reports

No incidents have been reported in humans, however, target species incident reports through December 1996 are as follows (From Memo of Virginia A. Dobozy, 4/1/97; D233461):

Product	Estimated No. of Treatments Sold*	No. of 6(a)(2) Reports Submitted to EPA	% of 6(a)(2) Reports vs. No. of Treatments Sold
Frontline® Spray Treatment	5,433,744	21	0.0004
Frontline® Top Spot™ for Cats	1,387,410	15	0.0011
Frontline® Top Spot™ for Dogs	3,960,810	13	0.0003
Total Frontline® Products	10, 781,964	49	0.0005

* Treatments sold estimated using the average weight of a cat = 8 lbs. and the average weight of a dog = 30 lbs.

c. Statement of the adequacy of the residential exposure data base to assess infants' and children's exposures

The residential (food and water) exposure database for fipronil is adequate to assess infants' and children's exposure.

5. Aggregate Exposure and Risk Assessment/Characterization

a. Acute Aggregate Exposure and Risk

From the acute dietary (food only) risk assessment, a high-end exposure estimate of was calculated for these subgroups: females 13+ years, for the general U.S. population, infants (< 1 year), children (1-6 years), and males 13+. The following table shows the high end exposure and total dietary (food only) MOEs of these population subgroups.

Subgroup	High-End Exposures (mg/kg/day)	MOE
General U.S. Population	0.0018	278
Infants (< 1 year)	0.003	167
Children (1-6 years)	0.003	167
Females (13+ years)	0.0012	417
Males (13+ years)	0.0014	357

The maximum estimated concentrations of fipronil in surface and ground water are less than OPP's levels of concern for fipronil in drinking water as

a contribution to acute aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of fipronil in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of fipronil in surface waters and ground waters to levels of concern for fipronil in drinking water. The estimates of fipronil in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of fipronil on drinking water as a part of the aggregate acute risk assessment process.

b. Short- and Intermediate- Term Aggregate Exposure and Risk

The short- and intermediate-term NOEL for dermal exposure is based on a dermal exposure toxicity study. The dietary (oral) exposure is adjusted for an oral endpoint (from the developmental study) so that it can be compared to the dermal endpoint. The NOEL from the oral developmental study (0.05 mg/kg/day) is 100-fold lower than that of the 21-day dermal study (5 mg/kg/day).

The adjusted chronic dietary exposure from fipronil is thus 0.0023 mg/kg/day (ARC f 0.000023 mg/kg/day multiplied by 100). The calculated fipronil dietary MOE for children (1-6 years old) is 2,170 (short tem NOEL of 5 mg/kg/day divided by adjusted dietary exposure of 0.0023 mg/kg/day). The adjusted chronic dietary exposure from MB 46513 is thus 0.001 mg/kg/day (ARC f 0.000001 mg/kg/day multiplied by 1000). The calculated MB 46513 dietary MOE for children (1-6 years old) is 5,000 (short tem NOEL of 5 mg/kg/day divided by adjusted dietary exposure of 0.0001 mg/kg/day). The adjusted oral residential exposure is 0.01 mg/kg/day (oral ingestion of 0.0001 mg/kg/day multiplied by 100). The dermal residential exposure is 0.005 mg/kg/day. Therefore the total residential exposure is 0.015 mg/kg/day. The calculated dietary MOE for children (1-6 years old) is 330 (short-term NOEL of 5 mg/kg/day divided by adjusted dietary exposure of 0.015 mg/kg/day).

For the short- and intermediate-term aggregate risk of the most highly exposed subgroup (children 1-6 years), the calculated MOE is 270 (reciprocal of the sum of the reciprocal food and residential). There is a potential for short- and intermediate-term exposure from drinking water.

However, as estimated average concentrations of fipronil in surface and ground water are less than OPP's levels of concern for drinking water as a contribution to chronic aggregate and chronic exposures, contribution to short- and intermediate- term exposure should not exceed OPP's levels of concern either.

c. Chronic Aggregate Exposure and Risk

For the U.S. population, 6.5% of the RfD is occupied by dietary (food) exposure. Though fipronil is currently registered for residential uses, no chronic residential exposure is anticipated. The estimated average concentrations of fipronil in surface and ground water are less than OPP's levels of concern for fipronil in drinking water as a contribution to chronic aggregate exposure. Therefore, OPP concludes with reasonable certainty that residues of fipronil in drinking water do not contribute significantly to the aggregate chronic human health risk at the present time considering the present uses and uses proposed in this action.

OPP bases this determination on a comparison of estimated concentrations of fipronil in surface waters and ground waters to levels of concern for fipronil in drinking water. The estimates of fipronil in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of concern in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of fipronil on drinking water as a part of the aggregate chronic risk assessment process.

6. Other Food Quality Protection Act (FQPA) Considerations

a. Cumulative Risk

Fipronil is structurally similar to other members of the pyrazole class of pesticides (i.e., tebufenpyrad, pyrazolynate, benzofenap, etc.). Further, other pesticides may have common toxicity endpoints with fipronil.

Section 408 of FQPA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency considers "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." While the Agency has some information in its files that may be helpful in determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to resolve the

scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will enable it to develop and apply policies for evaluating the cumulative effects of chemicals having a common mechanism of toxicity. At present, however, the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments. There are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

EPA does not have, at this time, available data to determine whether fipronil has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that fipronil has a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether fipronil share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for fipronil need to be modified or revoked.

b. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...". The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disrupter effects.

c. Determination of Safety

US Population, Infants, and Children

The acute dietary (food only) MOE for females 13+ years old (accounts for both maternal and fetal exposure) is 360. This MOE calculation was based on an acute neurotoxicity study (MRID# 42918635) NOEL in rats of 0.5 mg/kg/day for fipronil and 0.05 mg/kg/day for MB 46513. This risk assessment assumed 100% crop treated for all treated crops consumed, resulting in a significant over-estimate of dietary exposure. Despite the potential for exposure to fipronil in drinking water, HED does not expect the acute aggregate exposure to exceed OPP's level of concern. The large acute dietary MOE calculated for females 13+ years old provides assurance that there is a reasonable certainty of no harm for both females 13+ years and the pre-natal development of infants.

Using the exposure assumptions described above, HED has concluded that the percentage of the RfD that will be utilized by chronic dietary (food only) exposure to residues of fipronil ranges from 5.1% for nursing infants less than one year old, up to 16.7% for non-nursing infants less than one year old. Despite the potential for exposure to fipronil in drinking water, HED does not expect the chronic aggregate exposure to exceed 100% of the RfD. There are uses of fipronil that result in residential exposure, but is not expected to result in chronic exposure. HED concludes that there is a reasonable certainty that no harm will result to infants and children from chronic aggregate exposure to fipronil residues.

7. Data Requirements

a. Toxicology

There is currently only one toxicology data gap for **fipronil**, its metabolites or the **photodegradate**. This is the acute inhalation study with the ICON™6.2FC formulation. The Registrant should submit the positive control data for the acute rat neurotoxicity study with the **photodegradate** so this study can be upgraded to acceptable (this may be in RD for inprocessing at this time). In addition, the Registrant should submit a chronic study on the **photodegradate (MB 46513)** if one is completed.

b. Chemistry

I. The proposed feeding/grazing restrictions on rice straw are not practical and must, therefore, be removed from the labels. A revised Section B must be submitted.

ii. The petitioner should submit one additional rice residue trial located in region 5.

iii. To provide for the periodic evaluation of the anticipated residues, the

Agency will require under Section 408(b)(2)(E) residue data be submitted every five years as long as the proposed tolerances remain in force.

iv. A revised Section F should be submitted amending the proposed tolerance for rice grain to 0.04 ppm.

v. Storage stability data for the metabolite MB 46513 should be submitted.

c. Occupational and Residential Exposure

I. No additional data are required for this use.

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